Object-Location Memory in Old Age: Brain and Cognitive Plasticity Induced by a Process-Based Training

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“Memory isn't something that stays with you at all times. It's a quantity that gets summoned or evoked or brought to mind.
It gets carried to an arena for our viewing pleasure.
By definition, then, there are times it must go missing.”
J. Picoult, Vanishing Acts

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ABSTRACT

This thesis focuses on object-location memory (OLM), a subtype of spatial episodic memory, that enables us to remember where we have stored our keys, left our wallet, or parked our car. While these examples illustrate the high relevance of OLM for everyday functioning, it is a fact that OLM deficits accumulate with progressing age. Thus, there seems to be a great demand for tailor-made interventions that mitigate these impairments. A process-based cognitive training targeting OLM seems to be a particular promising approach. There is evidence that this type of training leads to improved cognitive performance, transfer to untrained abilities as well as maintenance of training-induced increments in healthy older adults.

The first article, a review of 31 studies, identified brain regions involved in OLM and their changes across adulthood. Both lesion and neuroimaging studies with healthy young adults demonstrated that the inferior temporal gyrus/fusiform gyrus, the posterior parietal cortex, and the parahippocampal gyrus are critical for OLM. The neuroimaging studies on age differences indicated that healthy older adults activated relevant brain regions less strongly than young adults. Instead they recruited corresponding brain regions in the contralateral hemisphere or additional structures that have not been found to be specialized for OLM in young adults.

The study described in the second article investigated a process-based OLM training of six weeks in healthy older adults (60–75 years) in terms of training gains, transfer to untrained cognitive abilities, and maintenance. A cognitive testbattery measuring transfer was administered before, in the middle of, and after the training as well as four months later. Results yielded a significant linear increase in training task performance for participants who completed the OLM training compared to the active control group who was administered a non-adaptive visual perception training. Analyses addressing training-related changes in

untrained tasks revealed for OLM participants significant near transfer which was maintained until four months after training termination. Thus, the OLM training improved its targeted ability but also other spatial episodic memory skills enduring in older adults.

Based on the same training study, differential brain activation changes were examined in the third article with functional magnetic resonance imaging (fMRI) while participants solved an untrained OLM task in the scanner. Across the training period, both training groups demonstrated activity increases in occipito-parietal brain regions critical for object-location perception accompanied by decreases in frontal regions. Contrary to the active control training, the OLM training induced continuous reduction of brain activity during encoding in executive control regions. Moreover, activity decreases in OLM relevant brain regions in the second part of the training indicated progressive automation of task-inherent processes. Together, these findings shed light on neural plasticity induced by a process-based OLM training in old age.

ZUSAMMENFASSUNG

Diese Dissertation fokussiert auf das Ortsgedächtnis von Objekten (OLM), einem Subtyp des räumlich-episodischen Gedächtnisses, welches es ermöglicht, uns zu erinnern, wo wir unsere Schlüssel aufbewahrt, unsere Brieftasche hingelegt oder unser Auto geparkt haben. Diese Beispiele illustrieren die hohe funktionelle Relevanz des OLM für den Alltag. Aufgrund des fortschreitenden Nachlassens des OLM im Alter sind massgeschneiderte Interventionen, die dieser Entwicklung entgegen wirken, von grosser Bedeutung. Ein kognitives Prozesstraining des OLM scheint ein besonders vielversprechender Ansatz zu sein. Es gibt deutliche Hinweise, dass diese Art des Trainings zu Leistungssteigerungen in den Trainingsaufgaben sowie zu nachhaltigen Verbesserungen in anderen, untrainierten kognitiven Fähigkeiten (Transfer) bei gesunden älteren Erwachsenen führt.

Im ersten Artikel, einer Übersichtsarbeit von 31 Studien, wurden OLM relevante Hirnregionen identifiziert und deren altersbedingte Veränderungen festgehalten. Sowohl Läsionsstudien als auch Studien mit bildgebenden Verfahren bei gesunden jungen Erwachsenen zeigten, dass der inferiore Gyrus temporalis/Gyrus fusiformis, der posteriore Parietalcortex und der Gyrus parahippocampalis für das OLM von Bedeutung sind. Die altersvergleichenden Studien konnten verdeutlichen, dass diese Hirnregionen bei gesunden älteren Erwachsenen weniger stark aktiviert waren als bei jüngeren. Stattdessen zeigten sie Aktivierungen in kontralateralen Hirnregionen oder in zusätzlichen Strukturen, die bei jungen Erwachsenen nicht nachgewiesen wurden.

Die Studie, die im zweiten Artikel beschrieben wird, untersuchte die Wirksamkeit eines 6-wöchigen Prozesstrainings des OLM bei gesunden älteren Erwachsenen (60–75 Jahre) in Bezug auf Leistungsverbesserungen in den Trainingsaufgaben, Transfer auf nicht trainierte kognitive Fähigkeiten und die Aufrechterhaltung der Leistungsgewinne. Sitzungen, in denen kognitive Testbatterien zur Messung des Transfers eingesetzt wurden, fanden vor, während

des und nach dem Training sowie vier Monate nach dessen Ende statt. Die Experimentalgruppe, die das OLM Training abgeschlossen hatte, wies signifikante lineare Verbesserungen in der Trainingsleistung auf. Im Gegensatz zur aktiven Kontrollgruppe, die ein nicht adaptives Training der visuellen Wahrnehmung absolviert hatte, steigerte sich die Experimentalgruppe auch signifikant in nahen Transferaufgaben. Dies konnte vier Monate nach Trainingsende noch nachgewiesen werden. Diese Ergebnisse deuten darauf hin, dass ein Prozesstraining des OLM nicht nur die trainierte Fähigkeit, sondern auch räumlich-episodische Gedächtnisleistungen bei älteren Erwachsenen verbessert.

Ausgehend von derselben Trainingsstudie wurden im dritten Artikel Veränderungen der Hirnaktivität mittels funktioneller Magnetresonanztomographie (fMRT) untersucht, während eine untrainierte OLM-Aufgabe im Scanner gelöst wurde. Beide Trainingsgruppen zeigten im Verlauf des Trainings Aktivitätszunahmen in Regionen des Okzipital- und Parietalcortex, in Regionen also, die für die Ortserkennung von Objekten entscheidend sind. Diese gingen einher mit einer Abnahme von Hirnaktivität in frontalen Regionen. Im Vergleich zur aktiven Kontrollgruppe war in der Experimentalgruppe eine kontinuierliche Reduktion der Hirnaktivität in exekutiven Kontrollregionen während des Enkodierens zu beobachten. Ebenfalls wurde im zweiten Teil des Trainings in OLM relevanten Hirnregionen reduzierte Aktivität nachgewiesen, was auf eine Automatisierung der beanspruchten kognitiven Prozesse hindeutet. Diese Ergebnisse zeigen auf, dass ein Prozesstraining des OLM im Alter neuronale Plastizität fördert.

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1 INTRODUCTION

As the proportion of individuals aged over 65 in the population grows and is predicted to continue to increase (Giannakouris, 2008; Lanzieri, 2011), there is a pressing need – from both a societal as well as economic viewpoint – to promote cognitive health and functional independence in this group. Normal aging has been associated with a deterioration of brain structure and function (Hedden & Gabrieli, 2004) as well as a decline in cognitive abilities in multiple domains (e.g., Rönnlund, Nyberg, Bäckman, & Nilsson, 2005; Schaie, 2005). However, cognitive health has been denoted by older individuals as an essential contributor to successful aging and for quality of life (Reichstadt, Depp, Palinkas, Folsom, & Jeste, 2007). Hence, interventions intended to delay age-related cognitive decline are clearly of great interest. Based on the notion that cognitive plasticity is possible across the lifespan (Noack, Lövdén, Schmiedek, & Lindenberger, 2009; Willis, Schaie, & Martin, 2009), mentally stimulating activities such as cognitive training have the potential to maintain or improve cognitive functioning in everyday life (Hertzog, Kramer, Wilson, & Lindenberger, 2008). Within this context, memory training has shown to be beneficial to improving memory performance in older adults (Lustig, Shah, Seidler, & Reuter-Lorenz, 2009; Rebok, Carlson, & Langbaum, 2007). With regard to self-perceived memory abilities, one of the most common complaints of older adults is that they cannot remember where they have placed personal belongings (Ossher, Flegal, & Lustig, 2013), self-observations with which empirical research generally agrees (Kessels & Postma, 2006; Uttl & Graf, 1993). In reference to the applicability of the so-called object-location memory (subsequently abbreviated as OLM) in real-life situations, the present thesis focuses on the plasticity of this type of memory in old age in terms of cognitive and neural effects.

The first part of the introduction provides a definition of OLM and outlines the reasons why this type of memory deserves special attention in the aging research. In addition, brain

regions involved in OLM are described and how they are affected by aging. Furthermore, it addresses cognitive training as a tool to promote cognitive health, introduces different training approaches, and summarizes knowledge about behavioral and neural training effects in old age. It closes with methodological considerations. The second part of the introduction contains aims and research questions of the present thesis followed by three articles. The first article is a systematic review of findings from 31 empirical studies for the identification of brain regions involved in OLM. Both studies of patients with focal brain lesions and neuroimaging studies of healthy adults are included. Also, evidence of neural changes in relevant brain regions for OLM across adulthood is reviewed, and suggestions for future research are discussed. In the second article, the efficacy of an intensive process-based training of OLM in older adults is investigated with respect to training gains, transfer, and the maintenance of training effects. The third article augments these findings with neuroimaging data assessed with functional magnetic resonance imaging (fMRI). Thus, by presenting both cognitive and neural outcome measures, the two articles complete the picture of plasticity induced by a process-based OLM training. The thesis concludes with a general discussion on the findings of all three articles including possible theoretical, methodological, and practical implications for future work.

1.1 Object-Location Memory

In everyday life, people have to deal with tasks such as remembering where they have left their reading glasses and keys, or where they have parked their car. To successfully search for personal belongings in small- or large-scale surroundings, we considerably depend on OLM (Postma, Kessels, & van Asselen, 2008). Given these examples, it is obvious that OLM is a vital part of everyone's day-to-day life.

In the classical framework of memory models, OLM can be regarded as prototypical form of episodic memory. Episodic memory entails the capacity to encode, store, and retrieve personally experienced events (Tulving, 1972). More specifically, in addition to the content of the episode, temporal and spatial contextual details attached to the event are prominent facets of episodic memory (Tulving, 2002; Tulving & Markowitsch, 1998). Two interacting features are believed to subserve episodic memory functioning: The associative component refers to binding different aspects of an event into a cohesive memory trace during encoding, storage, and retrieval. In contrast, the strategic component manifests itself during encoding through organization or elaboration of to-be-remembered information about events and during retrieval through monitoring and evaluating the retrieved information with respect to its correctness and completeness (Moscovitch et al., 2005; Shing et al., 2010). Strategic processes can either be self-initiated or induced by external support such as instructions or the provision of retrieval cues (Kausler, 1994).

Importantly, a distinction needs to be made between OLM acquired by looking at the environment from static viewpoints and OLM acquired by spatial navigation, i.e., moving around. While the former mostly comprises a single perspective of the surroundings, the latter involves sequentially changing viewpoints that have to be integrated to grasp the overall layout of the environment and the locations of the objects within. Since navigation through the environment usually follows given routes, OLM acquired by spatial navigation can rely on non-declarative memory processes, i.e., implicit memory processes such as stimulus-response learning which depends on the conjunction of visual and movement-related cues (Burgess, 2008; Kessels, de Haan, Kappelle, & Postma, 2001; Postma et al., 2008). In this thesis, OLM is referred to as acquired from static viewpoints.

1.1.1 Reasons for Investigating Object-Location Memory

There are several reasons why OLM deserves high attention in research. First, as emphasized above, intact OLM is clearly essential for managing many everyday tasks. Impairments of this type of memory can result in severe limitations (Kessels & Postma, 2006). Thus, it is easily conceivable that deficits in OLM may hinder independent living as well as negatively affect a person's well-being. Furthermore, cognitive impairments are associated with increased health care costs (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Because it is of great concern for older individuals to stay cognitively healthy and to remain functionally independent (Duay & Bryan, 2006; Montross et al., 2006), promoting the integrity of OLM is of utmost relevance in old age. Second, behavioral research indicates that OLM declines significantly across adulthood, particularly in old age (Kessels & Postma, 2006; Uttl & Graf, 1993). OLM decline in older adults has also been discussed as an early sign of Alzheimer's disease (e.g., Alescio-Lautier et al., 2007). Therefore, it is clearly of interest to disentangle normal aging-associated changes of OLM from those caused by pathological degenerative neural changes. Moreover, the identification of changes in neural correlates of OLM across adulthood may facilitate the development of cognitive training interventions that specifically enhance the functioning of less efficient brain regions involved in OLM. From this knowledge, implications may be drawn on how to induce the compensatory use of other brain regions. Third, despite the practical relevance of OLM for everyday functioning, it remains understudied to date compared to other types of memory (i.e., verbal memory, memory for objects or faces) with regard to effects of aging, neural correlates, or training. Following on from this, it seems essential to gain a better understanding of all of these aspects of OLM in order to develop tailor-made interventions to successfully mitigate its age-related decline.

1.1.2 Brain Regions Involved in Object-Location Memory

Following Fodor (1983), theories about brain organization and function distinguish between domain-general and domain-specific brain structures (Coltheart, 1999; Moscovitch, 2000). Brain regions are referred to as domain-general if they can be defined by the function they serve, i.e., encoding and retrieval, irrespective of the information that is processed. In contrast, domain-specific brain modules are characterized by the type of information they process, e.g., verbal or spatial material.

For episodic memory – and as prototype of episodic memory also for OLM – the network of *domain-general regions* comprises a system of interconnected structures in the medial temporal lobe (MTL) including the hippocampus and the surrounding perirhinal, entorhinal, and parahippocampal cortices as well as regions of the prefrontal cortex (PFC) (Moscovitch et al., 2005). On the one hand, MTL regions, in particular the hippocampus, are believed to be essential for binding individual aspects of memories into conjoint representations and thereby are mediating recollective memories of contextually rich information (associative component). On the other hand, the PFC, especially ventrolateral PFC regions, are engaged in the selection, maintenance, and control of to-be-encoded information (strategic component) and as such interact with regions of the MTL (Blumenfeld & Ranganath, 2007; Simons & Spiers, 2003). Although differently contributing to successful episodic memory, structures of both the MTL and the PFC are thought to closely interact with one another to subserve episodic memory function (Simons & Spiers, 2003), a relationship which has been found to be stronger in older compared to younger adults (Dennis et al., 2008). While the crucial roles of the MTL and the PFC in episodic memory have long been established, the contributions of extra-hippocampal structures such as the perirhinal, entorhinal, and parahippocampal cortices are still inconclusive. Evidence from animal, lesion, and neuroimaging studies remains controversial as to their general involvement in episodic

memory, spatial memory, or exclusively in associative memory processes (Burgess, Maguire, & O'Keefe, 2002; Eichenbaum, 2000; Rugg & Yonelinas, 2003). More recent evidence suggests that the perirhinal cortex seems to be responsible for the encoding of memory items of an event, possibly also for the binding of multiple features of each of these items together, and for mediating recognition based on familiarity. Conversely, recollection-based retrieval processes rely on the hippocampus, the parahippocampal cortex, the medial PFC, the retrosplenial/posterior cingulate cortex as well as on the posterior parietal cortex (Davachi, 2006; Eichenbaum, Sauvage, Fortin, Komorowski, & Lipton, 2012; Rugg & Vilberg, 2013; Yonelinas, 2002). The potential roles of other brain regions involved in episodic memory such as the cingulate gyrus and the cerebellum are less specified, however, the interest in their contribution is growing (Spaniol et al., 2009).

Postma and colleagues (2004, 2008) proposed in their neurocognitive model three types of processes specific to OLM: object processing, location processing, and object-to-location binding. The authors further suggested that as *domain-specific regions* the ventral visual processing stream, notably the inferior temporal gyrus, supports object processing, while the dorsal visual processing stream, in particular the posterior parietal cortex, subserves location processing. In addition, they concluded that the hippocampus is mainly responsible for binding objects to locations. However, the authors based their research mainly on evidence from lesion studies as did Kessels and colleagues (2001) who investigated in their meta-analysis OLM deficits of patients with hippocampal lesions. In addition to evidence from lesion studies, findings from neuroimaging studies of young adults (e.g., Cansino, Maquet, Dolan, & Rugg, 2002; Johnsrude, Owen, Crane, Milner, & Evans, 1999; Owen, Milner, Petrides, & Evans, 1996b; Sommer, Rose, Gläscher, Wolbers, & Büchel, 2005a; Sommer, Rose, Weiller, & Büchel, 2005b) point to the critical involvement of other anterior or mediotemporal (e.g., parahippocampal gyrus) as well as frontal, occipital, and cerebellar

regions in OLM. In conclusion, previous empirical evidence indicates that key brain regions involved in OLM are mediotemporal and prefrontal regions as well as the inferior temporal cortex and the posterior parietal cortex.

With progressing age, the human brain undergoes considerable changes. The next section presents evidence on how normal aging affects brain regions in general and in particular those specific to OLM.

1.1.3 Healthy Aging and Object-Location Memory

Cross-sectional and longitudinal research has documented episodic memory decline with advancing age together with other cognitive functions such as working memory, reasoning, or spatial orientation (Cansino, 2009; Hoyer & Verhaeghen, 2006; Rönnlund et al., 2005; Schaie, 1996). However, there are large individual differences in the manifestation of these changes (Wilson et al., 2002) as well as with respect to the age of onset of the decline (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). Generally, memory for content is less affected by age, while the recollection of contextual characteristics has been shown to be particularly impaired (Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995). These findings are consistent with the associative binding deficit in old age (Naveh-Benjamin, 2000) which is apparent in difficulties of binding together features between different dimensions such as objects to locations (e.g., Chalfonte & Johnson, 1996). The associative deficit hypothesis has received support from numerous studies and in particular under intentional learning situations (Old & Naveh-Benjamin, 2008).

With increasing age, OLM function is also known to decline (Kessels & Postma, 2006; Uttl & Graf, 1993). Not surprisingly, one of the most common complaints of older adults is that they cannot recall the locations of objects (Bolla, Lindgren, Bonaccorsy, & Bleecker, 1991; Ossher et al., 2013), a fact which has been corroborated by evidence of several studies

in laboratory contexts (e.g., Chalfonte & Johnson, 1996; Kessels, Hobbel, & Postma, 2007) as well as in settings resembling more real-life situations (Caldwell & Masson, 2001; Shih, Meadmore, & Liversedge, 2012; Uttl & Graf, 1993).

Generally, healthy aging is associated with both progressive structural alterations (Fjell & Walhovd, 2010; Salthouse, 2011; Walhovd et al., 2011) and functional decline in the brain (Grady, 2012; Mahncke, Bronstone, & Merzenich, 2006). Structural brain changes mainly include reduction of brain volume with the largest changes in prefrontal and temporal cortices and subcortical regions such as the hippocampus, the thalamus, and the putamen as well as the expansion of the ventricular system (Fjell & Walhovd, 2010). In addition, neuroimaging research has provided ample evidence of functional changes in the aging brain. Compared to young adults, reduced brain activity in posterior brain regions accompanied by increased activity in additional prefrontal regions has been observed in older adults, the so-called Posterior-Anterior Shift in Aging (PASA; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). This increased brain activity is often bilateral in older adults in tasks for which young adults engage unilateral prefrontal resources and as a pattern of brain activation differences between young and older adults is referred to as Hemispheric Asymmetry Reduction in Older Adults (HAROLD; Cabeza, 2002). This reduced selectivity of responses in brain regions was introduced as a concept of dedifferentiation as one viable explanation for age differences in brain activation (Grady, 2012). Additional prefrontal regions could thus be recruited due to neural inefficiency in the use of neural resources. Conversely, over-recruitment has been interpreted as functional reorganization of neural networks to cope with cognitive demands rather than caused by regional structural deterioration in reference to the scaffolding theory of aging and cognition (STAC; Park & Reuter-Lorenz, 2009) as well as compensation (Rajah & D'Esposito, 2005; Spreng, Wojtowicz, & Grady, 2010). Accordingly, increased activity in brain regions in older adults has been observed for the same performance level as that of

young adults, or it has been found to correlate positively with task performance in older but not in younger adults (Dennis & Cabeza, 2008; Park & Gutchess, 2005; Zöllig & Eschen, 2009). Besides, compensatory mechanisms have also been explained by the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz & Cappell, 2008) whereby older adults recruit additional resources in bilateral PFC during episodic memory tasks at low levels of cognitive load. However, at higher cognitive loads, compensation is no longer effective which leads to similar or less activity in older compared to younger adults (e.g., Spaniol & Grady, 2012). Importantly, although the relationship between cognitive performance and activation of recruited brain regions has been established, findings usually only relate to a subset of brain regions (Eyler, Sherzai, Kaup, & Jeste, 2011). This is probably due to compensational mechanisms buffering decline in brain activation before cognitive decline becomes imminent (Park & Reuter-Lorenz, 2009; Stern, 2009). Indeed, functional decline may be a precursor of cognitive decline in old age (Beason-Held, Kraut, & Resnick, 2008).

For OLM, evidence of age-related brain changes is scarce. To our knowledge, only the study of Kukolja and colleagues (2009) reported anatomical differences of OLM specific brain regions for young and older adults. To this end, voxel-based morphometry (VBM) analyses demonstrated significantly greater gray matter volumes in young compared to older adults in bilateral insular, inferior prefrontal, superior parietal, and cerebellar cortices as well as in the bilateral fusiform gyrus. As for differences in brain activation, three studies investigated brain activity during the completion of OLM tasks in young and older adults (Kukolja, Thiel, Wilms, Mirzazade, & Fink, 2009; Meulenbroek et al., 2010; Schiavetto, Köhler, Grady, Winocur, & Moscovitch, 2002). Their reported main effect of age consisted of increased brain activity in OLM relevant brain regions such as the fusiform gyrus during encoding and the lateral superior parietal cortex and the hippocampus during retrieval of

OLM in young adults. While reduced activity in OLM specific brain regions during encoding (i.e., fusiform gyrus) was found in older adults, increased activity was observed concurrently in other brain regions such as the anterior cingulate gyrus during encoding of later correctly retrieved object-location associations. This structure has been proposed to be a control region proactively influencing the fulfillment of cognitive processes as well as to guide behavior by selecting the most relevant amongst currently available stimuli (Menon & Uddin, 2010; Weston, 2012). This specific activation of older adults may reflect their additional effort to successfully encode object-location associations. Besides, increased activity was observed in the superior temporal lobe, the basal ganglia, and the thalamus, indicating the use of differential strategies of older adults in order to complete OLM tasks.

Mentally stimulating activities such as cognitive training have been found to improve cognitive and functional abilities in old age (Lustig et al., 2009). The concept of cognitive training is presented in the next chapter and integrates different training approaches, their underlying mechanisms as well as the evaluation of findings with respect to behavioral and neural effects.

1.2 Cognitive Training

A large proportion of our population has reached the age where cognitive deficits become a concern, in particular when affecting functional capacity. Since older individuals strive to stay cognitively healthy and to remain functionally independent as long as possible (Duay & Bryan, 2006; Montross et al., 2006), the mitigation of cognitive deficits has become of great importance in the aging research.

A lifestyle rich of cognitive, social, and physical activities has been reported to positively affect cognitive performance in old age (Hertzog et al., 2008; Lövdén, Ghisletta, & Lindenberger, 2005). Convincing evidence has documented that the adult brain is capable of

life-long plasticity as a function of experience and training, meaning that brain structure and brain function change in response to cognitive challenges (Greenwood, 2007; Jäncke, 2009; Pascual-Leone, Amedi, Fregni, & Merabet, 2005). The emphasis on so-called experience-dependent plasticity has led to the investigation of the relationship between the engagement in cognitively stimulating tasks (e.g., cognitive training), cognitive performance, and brain plasticity. Cognitive plasticity refers to the individual's latent potential of cognitive change in response to environmental demands such as experimental interventions or challenging life events which require mechanisms of compensation, adaptation, or optimization (Martin & Zöllig, 2009; Noack et al., 2009; Willis & Schaie, 2009). These alterations can be observed on a behavioral level as performance changes and/or on a neural level following structural and functional changes. According to their theoretical framework, Lövdén and colleagues (2010) suggest that plastic changes in brain and behavior are the result of a mismatch between the environmental demands and the individual's supply, i.e., functional capacity. Consequently, plasticity is multidirectional and can develop in terms of improved performance if external demands are greater than the individual's inherent supply. As a result, plastic changes are triggered by this mismatch and, as a reactive change, structural alterations such as regional cortical thickening or myelination are set in progress (e.g., Engvig et al., 2010, 2012). However, if the individual's capacity exceeds the environmental demands, this process occurs in reverse. In other words, if the experienced environmental demands are lower than the individual's functional supply, the brain adapts in the opposite direction and performance may decrease (Lövdén et al., 2010). As a consequence, cognitive performance that remains stable over a certain time can be viewed as being in a balance between demand and supply. Importantly, the individual's functional capacity determines the possible range of plasticity in interaction with the environmental stimuli. While the practice of a highly challenging task may induce cognitive plasticity in an individual with large functional capacity, the repeated

completion of the same task fails to induce change in an individual with a smaller range of inherent functional capacity. Therefore, when aiming to trigger cognitive plasticity by a cognitive training, its tasks should include a continuous adaptation of difficulty level in order to avoid being too easy or too difficult. Consequently, the to-be-solved tasks remain within the individual's range of functional capacity and thus ensure the optimal mismatch between resources and their limitations (Lövdén et al., 2010; Riediger, Li, & Lindenberger, 2006).

As a specific type of cognitive activity, cognitive training aims to enhance cognitive functioning by repeated practice of standardized cognitive tasks over a circumscribed timeframe (Gates & Valenzuela, 2010; Martin, Clare, Altgassen, Cameron, & Zehnder, 2011; Rabipour & Raz, 2012). The main purpose of cognitive training is to improve or preserve cognitive abilities at a healthy level and to ensure maintenance of everyday functionality (Eschen, Zöllig, & Martin, 2012). Hence, the enhancement of cognitive abilities is preferrably of direct utility in day-to-day life. Accordingly, in order to overcome the artificial laboratory setting, cognitive training interventions should aim for the generalization of training effects to untrained abilities (Hertzog et al., 2008; Jolles & Crone, 2012; Noack et al. 2009).

1.2.1 Cognitive Training Approaches

Generally, two major training approaches can be distinguished. In strategy-based training, participants are taught strategies to improve performance in tasks in which they show diminished capacity such as verbal episodic memory. Hence, by following explicit instructions, task-related cognitive processes may be recruited more efficiently (Lustig et al., 2009; Rebok et al., 2007; Verhaeghen, Marcoen, & Goossens, 1992). Common mnemonic strategies include rehearsal, categorization, visual imagery, learning of associations (e.g., faces-names, objects-words), or the method of loci (Gross et al., 2012). The vast majority of strategy-based memory training interventions has focussed on episodic memory and

participants were asked to practice tasks such as verbal list learning. Contrarily, process-based training regimes target specific cognitive functions but without explicit strategies on how to solve the tasks. The enhancement of cognitive abilities is accomplished by exposing participants repeatedly to several tasks which engage the same underlying mechanisms, i.e., load on the same specific process (Lustig et al. 2009). So far, process-based training has mostly targeted facets of executive processes (Kueider, Parisi, Gross, & Rebok, 2012). Importantly, the mechanisms underlying training effects differ insofar as strategy-based training makes use of a top-down approach while process-based training builds on a bottom-up approach (Zelinksi, 2009). Moreover, while strategy-based training stimulates the recruitment of additional or more efficient processes through repeated use of strategies, process-based training enhances the efficacy of task-inherent cognitive processes and induces their automation through repeated practice with performance-adaptive task difficulty (Willis & Schaie, 2009).

It is worth mentioning that traditional cognitive training, namely strategy-based training, is mostly held in group settings and requires frequent face-to-face contact and the availability of appropriate locations. Also, these training interventions are executed by a trained instructor, which can lead to high economical costs. Conversely, computerized process-based training requires usually only one introductory session to familiarize participants with the training software and is thus less expensive. Furthermore, it is standardized in terms of duration, structure as well as feedback and allows participants more flexibility concerning time and location of their training protocol (Kueider et al., 2012).

After completion, the outcome of a cognitive training intervention is evaluated by taking into account several aspects. This process is described in the next section.

1.2.2 Evaluation of Training Effects

The efficacy of a cognitive training intervention can be appraised by the magnitude of gains in the trained cognitive ability, the scope of transfer, and the maintenance, i.e., the stability of training and transfer effects over time (Eschen, 2012; Eschen et al., 2012; Hertzog et al., 2008).

The *magnitude of training gains* can be determined in various ways, namely with respect to changes in accuracy, reaction time, error rate in the trained tasks (e.g., Dahlin, Bäckman, Neely, & Nyberg, 2009; Erickson et al., 2007), or by indication of the task difficulty level reached across training sessions (e.g., Brehmer et al., 2011). In addition, a criterion task can be implemented before and after the training intervention to take into account the fact that it is unlikely that all individuals exhibit similar initial capacity for the to-be-trained tasks (e.g., Brehmer, Westerberg, & Bäckman, 2012; Dahlin et al., 2009). As a consequence, an increase in difficulty level of the trained tasks may be confounded by the individual's inherent capacity and thus will not reflect real improvement. Possibly, a criterion task would quantify training gains more accurately. Training gains can also be estimated by making use of learning curves (Jolles & Crone, 2012). Finally, functional outcome measures assess the efficacy of a cognitive intervention on a neural level (Buitenweg, Murre, & Ridderinkhof, 2012; Lustig et al., 2009).

Furthermore, cognitive training aims to produce *transfer*, i.e., improvements in untrained cognitive abilities and everyday functioning. However, the lack of a generally valid definition of transfer distances – and thus arbitrary classifications of cognitive outcome measures assessing either near or far transfer – can be regarded as prominent causes for the as yet inconclusive findings on training transfer. Therefore, it is essential to carefully follow theoretical frameworks when planning to survey the transfer of a training regime to other cognitive domains (Papp, Walsh, & Snyder, 2009). One such example is the taxonomy by

Noack and colleagues (2009) whereby the scope of transfer to untrained tasks can be measured with well-defined distances between trained and untrained abilities. Based on the hierarchical model of human intelligence by Carroll (1993), which classifies human cognitive abilities into narrow and broad abilities, Noack and colleagues (2009) defined transfer distance as *near* if training and transfer tasks assess the same narrow cognitive ability, as *medium* if outcome measures target a different narrow ability than the trained narrow ability, but all are from the same broad ability, and as *far* if both transfer and training tasks measure abilities from different broad abilities. While the definition of transfer refers to the similarity between two tasks and their underlying processes (Noack et al., 2009), the authors propose not to operationalize transfer with a single task, but rather assess transfer effects with at least three tasks which measure the same cognitive ability. Only if transfer can be shown on a latent factor, one can assume successful generalization of a training intervention. Otherwise, transfer could arise from commonalities of surface variables such as stimulus material (Eschen, 2012).

Finally, with respect to long-term *maintenance*, training effects are evaluated by the slope of cognitive functioning from post-training to follow-up assessments months or years after the training.

Importantly, cognitive training studies not only differ in training approach, type, complexity and number of training tasks, frequency, or duration of training sessions, but also in methodological features such as randomization procedure, blinding, and characteristics of control groups (Rabipour & Raz, 2012). By including passive control groups, retest effects in outcome measures can be controlled, while the implementation of active control groups permits the additional control of unspecific influences on cognitive performance (being challenged by a cognitive intervention, receiving feedback, being in contact with study staff and other training participants). Ideally, training interventions of both experimental and

control groups should be as similar as possible to ensure that motivational and practice effects are reduced. In addition, a double-blind controlled study design minimizes subjective expectancy effects and stratified randomization (e.g., by age or gender) ensures the balance of treatment groups with respect to critical variables.

1.2.3 Behavioral Training Effects in Old Age

Strategy-based training has produced long-lasting effects on the trained tasks, but very limited generalization to untrained cognitive abilities and everyday activities. Numerous studies have reported small to medium improvements in trained tasks after strategy-based training compared to passive control groups or control groups completing non-cognitive tasks (Gross et al., 2012; Martin et al., 2011; Verhaeghen et al., 1992). For instance, findings from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study revealed that a strategy-based memory training led to performance improvements in the trained ability, namely verbal episodic memory (Ball et al., 2002; Willis et al., 2006). In addition, medium to large training gains induced by process-based performance-adaptive training have been demonstrated in older adults compared to passive or active control groups (Hindin & Zelinksi, 2012; Melby-Lervåg & Hulme, 2013; Morrison & Chein, 2011).

With respect to transfer, strategy-based training has been shown to produce seldom or only limited transfer to untrained tasks, however, the observed near transfer effects were larger than the observed retest effects in control groups (Gross et al., 2012; Lustig et al., 2009; Papp et al., 2009; Verhaeghen et al., 1992). One reason for the lack of transfer could arise from the fact that older adults – although they know how to appropriately use mnemonic strategies – rarely ever employ them spontaneously (Ranganath, Flegal, & Kelly, 2011). It has been suggested that the trained strategies are highly specific (Rebok et al., 2007) and as such are hardly applicable to other tasks or real-life demands (Cavallini, Pagnin, & Vecchi, 2003;

Lustig et al., 2009). In contrast, for process-based training, mostly near and even far transfer effects have been demonstrated (Hindin & Zelinksi, 2012; Melby-Lervåg & Hulme, 2013; Morrison & Chein, 2011; Shipstead, Redick, & Engle, 2012).

Regarding the stability of training and transfer effects over time, it has been found that older adults were able to maintain training-induced increments in training and transfer task performance up to six years after training completion (Eschen, 2012; Lustig et al., 2009). However, contrary to strategy-based training, very few process-based training interventions have so far conducted longitudinal follow-up assessments.

To date, only a small number of studies targeting OLM in older adults has been published. In the study by Hampstead and colleagues (2012a), cognitively healthy older adults and older patients with amnestic Mild Cognitive Impairment (aMCI) participated in three sessions of a strategy-based OLM training within two weeks and completed a similar OLM task with half trained and half untrained object-location associations, thus at best representing near transfer, before and immediately after the training as well as one month at follow-up. The active control group received the same training tasks but was not taught mnemonic strategies. Both healthy participants and patients of the training group improved more in the outcome measure(s) from pre- to post-training (medium effect) as well as from pre-training to follow-up (large effect) in comparison to the active control group.

The second study focused on practice-induced changes in OLM in younger and older adults (Noack, Lövdén, Schmiedek, & Lindenberger, 2013). OLM was practiced in 100 sessions whereby a fixed number of objects was serially presented in a 6x6-grid. In addition to the locations, participants had to memorize the presented order of the objects. Results indicated that the older adults' performance in the training task improved significantly from pre- to post-training (medium effect size), but the younger adults gained more than the older adults (large effect size). Moreover, while the older participants' training gains were limited

to memory for location only (large effect size for OLM), the younger participants improved memory for both location and order of objects. However, the training did not allow for performance-adaptive progression of task difficulty nor was a control group included.

1.2.4 Neural Training Effects in Old Age

While training-related plasticity can be observed on a behavioral level, its manifestation is also apparent in terms of functional brain changes. Induced by cognitive training, functional brain changes have been observed as both activity increases and decreases in regions associated with the trained cognitive processes. Generally, it has been suggested that activity *increases* could be the result of the adoption of new strategies, namely in brain regions supporting the newly applied additional or more efficient cognitive processes, while activity *decreases* are more likely a consequence of practice-related increase of efficiency of task-inherent cognitive processes in brain regions which are specialized for these processes (Eschen, 2012; Kelly & Garavan, 2005).

Neural effects of *episodic memory* training interventions have been reported in a few studies so far. In all these studies, strategy-based training was employed. If participants had been taught the method of loci, training-related activity increases were observed in young adults in the left fusiform gyrus during both encoding and retrieval, in the bilateral PFC during encoding as well as in the left parahippocampal gyrus and the left precuneus during free recall (Kondo et al., 2005). Nyberg and colleagues (2003) reported for young adults increased activity in left frontal regions and for young and older participants in left occipito-parietal regions during free recall. These brain regions are known to be involved in mental imagery and thus indicate the recruitment of new cognitive processes demanded by the use of the method of loci. Furthermore, in the two studies by Kirchhoff and colleagues (2012a, b), healthy older adults practiced semantic encoding strategies for wordlists which led to activity

increases mainly in left frontal regions (medial superior frontal gyrus, middle frontal/precentral gyrus, posterior inferior frontal gyrus) and in the left lateral temporal cortex during encoding (2012a) as well as in the bilateral hippocampus during recognition (2012b). Again, the brain regions that showed activity increases were those known to be involved in the newly adopted encoding strategy, that is, semantic processing during encoding and recollection of associated information during retrieval. In contrast, process-based training targeting executive functions in older adults generally leads to training-induced activity decreases in prefrontal and parietal regions with or without accompanying additional recruitment of striatal brain regions compared to active control groups (Brehmer et al. 2011; Dahlin, Neely, Larsson, Bäckman, & Nyberg, 2008; Erickson et al., 2007). This may reflect a shift from effortful processing depending on fronto-parietal brain regions to more automatic processing relying on subcortical regions during training.

Training-induced brain activation changes for OLM have been investigated in one of the studies already mentioned above. For healthy older adults, Hampstead and colleagues (2012b) reported increased activity in the right hippocampus for untrained stimuli during cued OLM recall from pre- to post-training. The hippocampus is thought to be predominantly involved in object-to-location binding (Postma et al., 2008).

The course of training-related brain activation changes as a consequence of cognitive training is largely unknown. With regard to temporal trajectories, so far distinct patterns of adaptation have been described for *motor* training, i.e., initial activation of brain regions involved in control processes followed by activity decreases in these areas due to progressive automation of the practiced task and accompanied by increases in task-relevant motor brain regions (Kelly & Garavan, 2005). Functional neuroimaging studies on *cognitive* training effects have mainly implemented pre-post-designs with or without additional follow-up assessments and mostly ignored the temporal trajectories of training-induced brain activation

changes across the training period. However, in order to improve our understanding of how training affects regional brain activity, neural changes need to be monitored at multiple occasions during the training. First empirical evidence of training-related activation patterns at multiple stages during the training period has been documented by Hempel and colleagues (2004). They observed in middle-aged participants who received a visuo-spatial working memory training of four weeks activity increases related to improved performance in fronto-parietal areas after two weeks of training followed by decreases until training termination. This inverse u-shaped function demonstrated that a limited amount of training resulted in an increased recruitment of fronto-parietal regions followed by decreased activity due to more extensive training. Furthermore, Kühn and colleagues (2013) provided evidence of a similar activation pattern following working memory training in young adults. Compared to an active control group who trained on easier tasks of constant difficulty, the experimental training group received an adaptive training which led to initial activity increases in task-inherent brain regions (striatum and putamen) after about one week of daily training followed by decreases in the same regions. In addition, a trend for a similar inverse u-shaped function for fronto-parietal activity was demonstrated for both training groups. The observed differences of activation patterns in motor and cognitive training could be related to the way how the tasks were trained, i.e., the repeated practice of tasks of constant difficulty vs. intensive training of tasks with a performance-adaptive variation of task difficulty. Also, it is important to consider how a particular point in time of the training affects the level of observed brain activity, that is, which learning stage has been captured. Together, the investigation of training-related functional changes, and especially their temporal trajectories can help to explain the particular activation patterns observed and to distinguish between mechanisms likely to be underlying those changes.

For a better understanding of the methods used in cognitive neuroscience, the next

section gives a brief overview by covering their strengths and weaknesses. It ends with a more detailed description of fMRI since this neuroimaging technique was used in the third article of this thesis.

1.3 Methodological Considerations

A number of cognitive neuroscience tools are available for the identification of brain regions involved in cognitive processes such as OLM, namely the lesion method and neuroimaging techniques such as electroencephalography (EEG), magnetencephalography (MEG), positron emission tomography (PET), and fMRI. Out of these instruments, the lesion method and PET will be described briefly, since studies using these methods were included in the first article of this thesis. As the neuroimaging technique of our choice for the third article of this thesis, fMRI will be discussed in more detail.

Generally, both the lesion method and brain imaging techniques are important for our understanding of human memory, however they also have weaknesses. The logic behind the lesion method assumes impaired cognitive function after damage to the brain structure on which the cognitive function relies (Gazzaniga, Ivry, & Mangun, 1998). As a result, patients should show worse performance in tasks depending on this specific process than healthy individuals. However, while deficits in task performance of patients clearly provide information about the involvement of brain regions in cognitive processes, inferences about the exact contributions of these brain regions cannot be drawn due to several limitations: 1) Brain lesions are rarely circumscribed to a specific brain region but affect several areas; 2) since the human brain is extensively interconnected, patients with a lesion to a single brain region may still suffer from deficits in several cognitive abilities; 3) large interindividual variability in brain structures is not only true for the healthy population but concerns also brain lesions in patients. Hence, the specificity of lesions does not allow for inferences about

the precise contributions of brain regions to a particular cognitive process; 4) finally, reorganization of brain function after brain damage is common and different brain regions may be recruited for accomplishing the same task after damage than before. Hence, conclusions about the relationship between brain lesions and impaired performance should be drawn with reasonable care (Coltheart, 1999; Gazzaniga et al., 1998).

In contrast, neuroimaging techniques such as PET and fMRI permit the visualization of cognitive processes in the brain by assessing changes in blood flow and blood oxygenation closely related to neural activity. Neural activity evokes an increase in oxygen and glucose metabolism which results in a local increase of blood flow to the regions of increased neural activity. This hemodynamic response occurs after a delay of 1–5 s, rises to a peak over 4–6 s, then falls and undershoots the initial value briefly before reaching the baseline level again. The change in regional cerebral blood flow (rCBF) alters the blood volume as well as the relative concentration of oxyhemoglobin and deoxyhemoglobin in the blood. As a consequence, neural activity can be indirectly assessed by measuring the hemodynamic response (Jäncke, 2005; Poeppel & Krause, 2008). While these techniques allow for in-vivo observation of cognitive processes, they also have drawbacks: 1) They are limited by the indirect measure of neural activity; 2) the resolution of hemodynamic measures is limited temporally due to the characteristics of the hemodynamic response by assessing neural activity most likely as an overall post-synaptic activity (Poeppel & Krause, 2008); 3) interpretations of findings may depend on the experimental design, i.e., data acquisition and image processing; 4) contrary to fMRI, which is not invasive, PET measures the rCBF by means of intravenously injected positron emitting perfusion tracers entering the brain. In conclusion, the combination of lesion and neuroimaging methods has the potential to complement both approaches with respect to their strengths and weaknesses and thus yields the most accurate information of the neural networks of interest.

Functional MRI localizes correlates of neural activity measured as regional cerebral blood oxygenation. Local capillary vasodilation leads to an overload of blood flow in relation to the demand for oxygen resulting in an increased ratio of oxygenated to deoxygenated hemoglobin. Due to the different magnetic properties of oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic), this change can be observed as blood-oxygen-level-dependent response, i.e., the BOLD signal. The presence of deoxygenated blood decreases the BOLD signal relative to the presence of oxygenated blood. However, these differences are small and depend on the field strength (e.g., 1.5 or 3 T). The sequence most commonly used for BOLD contrast imaging is echo-plannar imaging (EPI) which is optimized for the detection of the BOLD effect. Results comprise brain regions in which the intensity of the BOLD signal correlates with the timing of an experimental task. Activation maps are computed by overlaying color-coded statistical correlation values for the BOLD response on anatomical images (Hwang & Golby, 2006; Jäncke, 2005; Poeppel & Krause, 2008).

Functional MRI has become an important technique in neurocognitive science. It is non-invasive, has no side-effects and thus can be easily repeated. Furthermore, it allows for the systematic and direct exploration of neural substrates of cognitive functions such as memory processes in healthy individuals instead of depending on the appropriate location of brain lesions in patients. Moreover, fMRI has an excellent spatial resolution of several millimeters or less, in particular at high field strengths. However, compared to EEG, the temporal resolution is rather low and lies in the order of several seconds. In addition, head movements may make findings uninterpretable due to artifacts. Because fMRI relies on magnetic fields for image acquisition, the different magnetic characteristics of properties such as bone, brain tissue, and air can cause distortions and loss of BOLD signal in adjacent brain regions due to magnetic field inhomogeneity present at the boundary between brain tissue and nearby air filled cavities. These so-called susceptibility artifacts are particularly prominent in

inferior frontal, inferomedial, and inferolateral temporal regions and thus may interfere with MTL imaging. Finally, statistical analyses play a large role in the interpretation of fMRI data (Hwang & Golby, 2006).

Inferences about brain processes involved in cognition are being made on the basis of two types of analytic strategies: the subtraction method and the covariance analysis. The subtraction method builds on the assumption that distinct brain regions are involved in various functions. This method is implemented by comparing functional signals between two experimental conditions, i.e., the loci of the signal differences presumably describe brain regions differentially engaged in the two conditions (termed functional topography). The more recent introduction of covariance analysis is based on the assessment of functional interactions between brain regions of a neural network (termed functional connectivity). By applying path analysis or structural equation modelling, the influence that neural elements have on each other can be characterized and quantified (Krause et al., 2006).

In the third article of this thesis, we applied the subtraction method. This analysis allows for the decomposition of the physiological signal into components of interest, components of no interest, and residual error terms. Contributions of each effect are estimated using the general linear model (GLM). The estimates of parameters represent the mean activity associated with an experimental condition. Furthermore, with the use of contrasts, regional specific effects are calculated based on the subtraction of the parameter estimates. The significance of each contrast is computed with an *F*- or *t*-statistic with or without additional covariates under the assumption of a normal distribution and transformed into a Gaussian field. Comparisons are then carried out based on local deviations of the Gaussian field above a predefined statistical threshold. The resulting maps finally characterize activation foci, their peak, their spatial extent, or both (Krause et al., 2006).

2 AIMS AND RESEARCH QUESTIONS

Previous research on behavioral and neural plasticity induced by cognitive training has produced important findings and valuable insights, however it has also left many questions unanswered. This thesis attempts to fill certain research gaps and aims to answer some of these open questions.

The first article of this thesis is a systematic review of 31 empirical studies investigating brain regions involved in OLM and their functional changes across adulthood. It intends to highlight the significance of this special type of memory by summarizing the existing knowledge from 16 lesion and 15 neuroimaging studies with respect to key regions critically engaged in OLM function. Three of the 15 neuroimaging studies explore age effects on the neural underpinnings of OLM. Furthermore, this review attempts to identify possible implications for ameliorating OLM in healthy older adults, i.e., which brain regions involved in OLM are amenable to what type of training intervention.

The second article of this thesis aims to provide behavioral evidence of the feasibility and the efficacy of a process-based OLM training of 30 sessions with respect to the magnitude of training gains, the scope of transfer, and the maintenance of these effects across four months in older adults. Despite its key relevance for everyday independent functioning, OLM has been neglected in training research so far. In addition, episodic memory has been targeted mostly by strategy-based training. Hence, our study attempts to break new ground in the training literature by presenting first evidence of cognitive plasticity in healthy older adults induced by a process-based OLM training compared to an active control group. Moreover, the implementation of four measurement points across the study allows for the longitudinal investigation of training and transfer effects.

The third article of this thesis is based on the same OLM training study. To date, evidence of neuroplasticity induced by cognitive training is still inconclusive with regard to

the direction of brain activation changes, namely increases or decreases (Kelly & Garavan, 2005; Park & Bischof, 2013). Hence, this third article aims to identify brain regions affected by a process-based OLM training in older adults, and in particular, to explore training-related functional changes, i.e., temporal trajectories across the training period until four months later.

3 BRAIN REGIONS INVOLVED IN OBJECT-LOCATION MEMORY ACROSS ADULTHOOD: WHAT DO WE KNOW AND WHAT IS MISSING? [1]

3.1 Introduction

We all know and dread those moments when we are asking ourselves: Where did I leave my glasses, my keys, or my car? Successfully remembering the locations of such or other objects in our environment relies on a specific type of memory, the so-called object-location memory (OLM) (Postma et al., 2008).

The aim of this review is to summarize findings on brain regions involved in this ability, their changes across adulthood, and their amenability to cognitive training. This is interesting for several reasons. First, as highlighted above, intact OLM is essential for managing many everyday tasks. Impairments of this type of memory can therefore hinder independent living considerably. Second, despite the importance of OLM for everyday functioning, its neural correlates and their plasticity across adulthood are understudied in humans as compared to other types of memory (e.g., verbal memory, memory for objects, memory for faces), and research on this topic has been by far less often reviewed. Third, behavioral research on OLM indicates that it declines significantly across adulthood, particularly in old age (for reviews see Kessels & Postma, 2006; Uttl & Graf, 1993). Besides, OLM deficits in older adults have been discussed as an early sign of Alzheimer's disease (Alescio-Lautier et al., 2007). Hence, reviewing the available research on changes in neural correlates of OLM across adulthood may help to distinguish normal aging-associated changes from those caused by pathological degenerative neural changes in old age. Moreover, the identification of changes in neural correlates of OLM across adulthood may foster the development of cognitive training interventions that specifically enhance the functioning of

[1] A similar version of this chapter has been submitted for publication to „Neuropsychology Review" (Zimmermann & Eschen)

less efficient brain regions involved in OLM or facilitate the compensatory use of other brain regions in older adults. The fourth reason for our interest in the subject of this review is to gain an overview of already existing research on neural effects of cognitive training interventions targeting OLM to identify those which work and why as well as possible research gaps.

Previous knowledge about brain regions involved in OLM

Following Fodor (1983), the successful completion of cognitive tasks depends on the interaction of domain-general and domain-specific brain regions (Coltheart, 1999; Moscovitch, 2000). Brain regions are referred to as domain-general if they can be defined by the cognitive function they subserve irrespective of the type of information that is processed. In contrast, domain-specific brain regions are characterized by the type of information they process.

Domain-general brain regions involved in OLM

Domain-general brain regions involved in OLM are those supporting episodic memory function since – in the context of classical memory models – OLM can be regarded as prototypical type of episodic memory. Episodic memory refers to the capacity to encode, store, and retrieve personally experienced events (Tulving, 1972). More specifically, episodic memory is thought to include the content of the event itself but also the context in which it occurred. Hence, the encoding, storage, and retrieval of temporal and spatial contextual details of an event are prominent features of episodic memory (Tulving, 2002; Tulving & Markowitsch, 1998). Moreover, episodic memory involves conscious awareness of an event and its context and is therefore considered as a type of explicit memory (Moscovitch, 2000).

For research on episodic memory in humans, mainly tasks requiring intentional encoding and retrieval of events and their contexts have been used.

As prototypical type of episodic memory, OLM demands the encoding, storage, and retrieval of objects *and* their locations in a specific environment at a specific time. While it is possible to incidentally learn and retrieve the locations of objects in our present environments (implicit OLM), OLM in humans mainly depends on intentional encoding of target aspects such as the identities of objects, their locations as well as their spatial and temporal context into a conjoint memory trace and on the conscious retrieval of these memory traces. Consequently, our review will focus only on research involving intentional episodic OLM tasks.

Additionally, a distinction needs to be made between OLM acquired by glances at the environment from static viewpoints and OLM acquired by spatial navigation, that is, from moving around in the environment. While the former mostly comprises only a single perspective of the environment, the latter involves sequentially changing viewpoints that have to be integrated to grasp the overall layout of the environment and the locations of the objects in it. Since navigation through the environment usually follows given routes, OLM acquired by spatial navigation can rely on implicit memory processes such as stimulus-response learning by which the locations of objects are determined by a series of movements at certain landmarks or route junctions (Burgess, 2008; Kessels et al., 2001; Postma et al., 2008). Therefore, in the current review only studies investigating OLM acquired by static glances at the objects' environments are included.

Episodic memory functioning is supposed to be dependent on two interacting components, i.e., the associative component and the strategic component (for reviews see Moscovitch et al., 2005; Shing at al., 2010). The associative component refers to binding different aspects of an event into a cohesive memory trace during encoding, storage, and

retrieval. The binding processes can either occur between different features within memory items (e.g., the color and the shape of an object), between different memory items (e.g., objects and their locations), or between features of core memory items of an event and features of its context (e.g., location of objects and shape of their environment) (for reviews see Shing et al., 2010; Zimmer, Mecklinger, & Lindenberger, 2006). The associative component of episodic memory can be assessed by so-called associative, context, or source memory tasks. While associative memory tasks usually test retrieval of pairs of memory items such as word or picture pairs, context and source memory tasks typically measure memory for contextual features of memory items (e.g., background task or order in which they occurred, person who presented them). However, a closer look at the literature reveals that under the terms associative, context, or source memory, the binding between all types of features of an event and its context has been studied (Johnson, 2005; Mitchell & Johnson, 2009; Spencer & Raz, 1995). Hence, research on episodic OLM can be found under all three terms.

In contrast, the strategic component is thought to contribute to episodic memory function through strategic control processes during both encoding and retrieval. During encoding, they include the organization or elaboration of to-be-remembered information about events, while during retrieval they comprise the monitoring of retrieval processes as well as the evaluation of retrieved information for correctness and completeness (Miller & Cohen, 2001; Moscovitch, 2000; Moscovitch et al., 2005; Shing et al. 2010). These strategic processes can either be self-initiated or evoked by instructions or environmental support such as the provision of retrieval cues (Kausler, 1994).

While a distributed functional network of medial temporal lobe (MTL) regions including the hippocampus and its adjacent regions (i.e., the perirhinal, entorhinal, and parahippocampal cortices) has been found to be critical for the associative component of episodic memory, the prefrontal cortex (PFC) is regarded as essential for the strategic

component (for reviews see Moscovitch, 2000; Moscovitch et al., 2005; Shing et al., 2010). Although they contribute differentially to successful episodic memory, both MTL and prefrontal lobe structures are thought to closely interact with one another to subserve episodic memory function (Simons & Spiers, 2003).

Neuroimaging research has demonstrated that for different episodic memory processes different networks of mediotemporal and prefrontal brain regions are important. Morevoer, it has been found that during episodic memory encoding mainly left and during episodic memory retrieval mainly right prefrontal regions are activated. This led to the proposal of the Hemispheric Encoding Retrieval Asymmetry (HERA) framework (Nyberg, Cabeza, & Tulving, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994).

In addition, different episodic encoding processes appear to be mediated by different mediotemporal regions. The perirhinal cortex seems to be responsible for the encoding of memory items of an event and possibly also for the binding of multiple features of each of these items together, while the hippocampus is thought to be essential for the binding of different memory items to one another and/or for the binding of different memory items with contextual features of an event. The parahippocampal cortex has been found to be involved in both types of processes (Davachi, 2006).

Other brain regions also appear to play a role during encoding depending on how the to-be-remembered information is processed (e.g., visually or auditory, perceptually or semantically). Importantly, according to Craik and Lockhart (1972), the greater the depth of processing of different features of an event and its context during encoding, the more elaborate and stronger the resulting episodic memory traces. Whereas the perceptual processing of the event and its context features is regarded as shallow, the semantic processing occurs at a deeper level.

Similarly, different types of episodic memory retrieval seem to be supported by different networks of mediotemporal and prefrontal regions. Mainly three types of episodic memory retrieval have been distinguished: free recall, cued recall, and recognition. Free recall is thought to require more strategic memory processing than cued recall and cued recall more than recognition (Craik & McDowd, 1987). Consequently, while free and cued recall both depend on prefrontal and mediotemporal regions, only the latter appear to support recognition (Gabrieli, 1998; Moscovitch, 2000; Moscovitch et al., 2005).

Episodic memory retrieval has been classified into recollection- and familiarity-based processes. While recollection-based retrieval processes are considered to involve conscious retrieval of details about previous events and their contexts, familiarity-based retrieval processes only categorize features of events and their contexts as familiar or non-familiar. Based on this familiarity classification, an event and its features is judged as previously experienced or not. Following on from this, episodic memory tasks demanding free and cued recall require recollection-based retrieval processes, while recognition tasks can be solved by both recollection- as well as familiarity-based retrieval processes (for a review see Yonelinas, 2002). Previous research has shown that recognition on the basis of familiarity seems to be mediated by the perirhinal cortex, while recollection-based retrieval processes appear to rely on the hippocampus as well as on the parahippocampal, retrosplenial/posterior cingulate, medial prefrontal, and lateral parietal cortices (Eichenbaum et al., 2012; Rugg & Vilberg, 2013; Yonelinas, 2002).

With regard to cued recall or recognition, the involved brain regions will vary with respect to the type of processing the retrieval cues evoke. If resembling the processing that was required during encoding, patterns of neural activity elicited during retrieval will overlap with those observed during encoding, otherwise different brain regions specialized for the type of processing used during retrieval will be active (Rugg, Johnson, Park, & Uncapher,

2008). Thus, depending on the phase (encoding or retrieval), the nature of the employed processes at these stages as well as the type of retrieval required, a different network of mainly mediotemporal and prefrontal but also of other cortical brain regions will be involved in OLM.

Domain-specific brain regions involved in OLM

Postma and colleagues (2004, 2008) proposed in their neurocognitive model of OLM that OLM involves three types of domain-specific processes: object processing, location processing, and object-to-location binding. Based on their review on previous research on brain regions involved in OLM with an emphasis on lesion studies, they concluded that regions of the ventral visual processing stream, namely the inferior temporal gyrus, support object processing, while regions of the dorsal visual processing stream, in particular the posterior parietal cortex, subserve location processing. For object processing, the authors proposed a special involvement of regions in the right hemisphere, but also suggested an additional activation of left hemisphere regions if the OLM task allows verbal processing of the objects.

With regard to location processing, Postma and colleagues (2004, 2008) distinguished between two types of reference frames and two types of spatial relations by which an object's location in space can be described. Egocentric reference frames describe the object's location in relation to the observing person's body, while allocentric reference frames characterize its location in relation to other objects or defining features of the environment. Egocentric location processing has been found to rely especially on the posterior parietal cortex, whereas the hippocampus and the parahippocampal cortex seem to be essential for allocentric location processing (Burgess, 2008; Burgess et al., 2002; Moscovitch et al., 2005).

Spatial relations of objects with regard to the two types of reference frames have been divided by Postma and colleagues (2004, 2008) following Kosslyn and colleagues (1987, 1992) into categorical and coordinate relations. Categorical relations define the locations of objects in an abstract broad sense (e.g., above, below, right, left, inside, outside), whereas coordinate relations specify the location coordinates of objects using exact metric distances (e.g., 3 cm below and 2 cm right from the corner). Categorical location descriptions have been found to rely on the left posterior parietal cortex, while coordinate location definitions seem to be supported by the right posterior parietal cortex (for a review see Jager & Postma, 2003).

In addition, Postma and colleagues (2004, 2008) came to the conclusion that the hippocampus is mainly responsible for binding objects to locations. The authors proposed a stronger involvement of the left hippocampus when objects are bound to categorical locations and a greater contribution of the right hippocampus when objects are bound to coordinate locations, however, they did not find clear empirical evidence for this suggestion.

In a meta-analysis on spatial episodic memory deficits of patients with hippocampal lesions, Kessels and colleagues (2001) demonstrated significant OLM impairments which were more pronounced in patients with right hippocampal lesions. This is probably caused by the fact that in research on OLM mainly tasks requiring allocentric location processing are employed.

In conclusion, previous empirical evidence indicates that key brain regions engaged in OLM are mediotemporal and prefrontal regions as well as the inferior temporal cortex and the posterior parietal cortex. Among mediotemporal regions, the hippocampus appears to be particularly involved in OLM. Depending on the subtype of the OLM task (e.g., requiring free recall, cued recall, or recognition; demanding categorical or coordinate location processing), different subsets of the above regions seem to be activated.

To our knowledge, a systematic review on research about brain regions involved in OLM in adulthood has so far been missing. Previous attempts (Kessels et al., 2001; Postma et al., 2008; Postma, Kessels, & van Asselen, 2004) focused on reviewing lesion studies and have not or only to a small degree included functional neuroimaging studies. Furthermore, they have been published some years ago, so meanwhile new studies may have been conducted. Therefore, the first aim of this work is to systematically search the available literature up to now and to review lesion and functional neuroimaging studies on episodic OLM to determine if previously proposed key brain regions really support OLM and which are specialized for subtypes of OLM.

Previous knowledge about changes in brain regions involved in OLM across adulthood

Changes in domain-general brain regions involved in OLM across adulthood

With progressing age, episodic memory declines along with other cognitive functions such as working memory, reasoning, or spatial orientation (for reviews and meta-analyses see Hoyer & Verhaeghen, 2006; Old & Naveh-Benjamin, 2008; Rönnlund et al., 2005; Schaie, 1996; Verhaeghen & Salthouse, 1997). Several theories have proposed that aging-associated episodic memory decline is above all based on impairments in forming and retrieving associations between simultaneously processed units of information (Burke & Light, 1981; Chalfonte & Johnson, 1996). This so-called associative binding deficit (Naveh-Benjamin, 2000) manifests itself in older adults' difficulties in binding together different features of events and their contexts such as faces and names (Naveh-Benjamin, Guez, Kilb, & Reedy, 2004; Sperling et al., 2003), objects and colors (Park & Puglisi, 1985), or pairs of words (Naveh-Benjamin, 2000). The associative deficit hypothesis has received support from a plethora of studies and can be particularly observed under intentional learning situations (for a meta-analysis see Old & Naveh-Benjamin, 2008).

Besides, strategic episodic memory processes also decline with age (Shing et al., 2010). Among different episodic memory encoding and retrieval processes, recollection has been found to be especially sensitive to effects of aging. Hence, in recognition tasks, older adults have been found to rely more on familiarity-based than recollection-based processes during retrieval (Yonelinas, 2002).

The decline in episodic memory function across adulthood has been related to reduction of both structural and functional integrity of relevant brain regions. Age-related structural white and gray matter changes are known to early and strongly affect the PFC. Furthermore, the hippocampus exhibits substantial structural decline in old age and to a lesser extent also its surrounding mediotemporal areas (for reviews see Fjell & Waldhovd, 2010; Raz & Rodrigue, 2006; Salthouse, 2011).

Interestingly, neuroimaging studies comparing young and older adults have demonstrated decreases of brain activity in mediotemporal regions, but also increases of activity in prefrontal regions during episodic memory tasks in older adults (for reviews see Dennis & Cabeza, 2008; Maillet & Rajah, 2013; Park & Gutchess, 2005; Park & Reuter-Lorenz, 2009). These findings are in line with two major observed patterns of brain activation differences between young and older adults. The first refers to the so-called Posterior-Anterior Shift in Aging (PASA; Davis et al., 2008) in which reduced activity in posterior brain regions involved in the perception and identification of the to-be-encoded material is coupled with increased prefrontal activity. The second pattern has been named Hemispheric Asymmetry Reduction in Older Adults (HAROLD) and describes a reduction of mediotemporal activity accompanied by additional activity in contralateral homogenous prefrontal brain regions (Cabeza, 2002). The additional recruitment of prefrontal areas in old age has been interpreted as either neural inefficiency or compensatory plasticity. While neural inefficiency explains the over-recruitment as reduced processing efficiency of the aging brain,

compensatory plasticity interprets the additional prefrontal recruitment as an effort to maintain performance despite functional declines in the MTL. In fact, recent findings confirm that the additional employment of prefrontal regions in episodic memory tasks by older adults is related to aging-associated hippocampal volume loss (Rajah, Languay, & Grady, 2011).

Changes in domain-specific brain regions involved in OLM across adulthood

Older adults show deficits in OLM in comparison to younger adults in laboratory contexts (Chalfonte & Johnson, 1996; Cherry & Park, 1993; Cooney & Arbuckle, 1997; Kessels et al., 2007; Light & Zelinski, 1983; Park, Cherry, Smith, & Lafronza, 1990; Puglisi, Park, Smith, & Hill, 1985; Sharps & Gollin, 1988) as well in settings resembling more real-life situations (Caldwell & Masson, 2001; Shih et al., 2012; Uttl & Graf, 1993). Besides, it has been demonstrated that middle-aged adults already perform worse than younger adults in OLM tasks (Uttl & Graf, 1993).

In addition, it has been found that other domain-specific brain regions involved in OLM (i.e., the inferior temporal cortex and the posterior parietal cortex) are also subject to age-related structural and functional decline, but earlier and to a lesser degree than the hippocampus (Raz et al., 2005).

Generally, neuroimaging studies on activation changes of brain regions supporting OLM across adulthood or on brain activation differences between young and older adults during OLM tasks seem to be scarce. Therefore, the second aim of this review is to identify and analyze such studies to summarize present knowledge about changes in brain regions involved in OLM across adulthood.

Previous knowledge about brain regions affected by OLM training across adulthood

The possible mitigation of older adults' episodic memory deficits through cognitive training interventions is an important area of aging research. Numerous studies documented that episodic memory training enhances episodic memory performance in healthy older adults. To date, memory training has mainly focused on teaching and practicing new strategies (e.g., method of loci, mental imagery) (for meta-analyses see Gross et al., 2012; Verhaeghen et al., 1992), whereas some newer training interventions have been successful in improving episodic memory by repeated practice of specific episodic memory tasks (for a review see Lustig et al., 2009). To our knowledge, there is only one study on a strategy-based training (Hampstead et al., 2012a) and one study on a practice-based training (Noack et al., 2013) targeting OLM. Both demonstrated that older adults significantly improved their OLM performance after repeated use of a new OLM strategy or after intensive practice of an OLM task.

Neural effects of episodic memory training have so far seldomly been investigated. First studies found increased brain activity in young adults after instruction and practice of the method of loci for a verbal memory task in the left fusiform gyrus for both encoding and retrieval phases, in the bilateral PFC during encoding, and in the left parahippocampal gyrus and the left precuneus during retrieval in the study by Kondo and colleagues (2005). Nyberg and colleagues (2003) observed a similar pattern in occipito-parietal regions in young and older adults during retrieval. In addition, a training teaching the same memory strategy induced significant changes in cortical thickness in older adults. In fact, the increased thickness of the right fusiform gyrus and the right lateral orbitofrontal cortex correlated positively with verbal memory improvement (Engvig et al., 2010). Furthermore, a positive correlation was observed between training-related memory improvement and increases of white matter integrity of association fibers, in particular of the anterior thalamic radiation and

the inferior occipito-frontal and uncinate fasciculi in the left hemisphere (Engvig et al., 2012). Finally, Lövdén, Schaefer and colleagues (2012) provided evidence that intensive practice of spatial navigation results in enhanced navigational performance and stable hippocampal volume across a four-month training period and until four months later at follow-up. In contrast, the active control group displayed declines in hippocampal volumes across the study period. The magnitude of hippocampal volume reduction in the control group corresponded to the typically observed age-related decline in this age group.

Since the study of brain activation changes induced by cognitive training generally is a relatively new research topic, the third aim of our review is to search for studies focusing on brain activation changes caused by OLM training regimes in adults and to use their findings to identify which brain regions involved in OLM are amenable to which type of training intervention.

Scope of this review

To accomplish the first aim of this review, that is to identify brain regions involved in episodic OLM, we systematically searched for lesion studies as well as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies with healthy young adults employing intentional non-navigational episodic OLM tasks. To realize the second aim of our review, that is the characterization of changes in brain regions involved in episodic OLM across adulthood, we examined the literature for fMRI and PET studies in which the same healthy adults had to complete intentional non-navigational episodic OLM tasks at different time points during their adulthood or in which groups of differentially aged healthy adults engaged in such tasks. Finally, to fulfill the third aim of this review, that is to investigate which brain regions involved in episodic OLM are affected by which type of episodic OLM training in adulthood, we searched for fMRI and PET studies on activation

changes induced by cognitive training targeting intentional non-navigational episodic OLM in healthy adults.

3.2 Methods

Literature search

This review focuses on original research on 1) brain regions involved in intentional non-navigational episodic OLM in the adult human brain, 2) on age-related changes in these brain regions across adulthood, and 3) on changes in these brain regions induced by cognitive training targeting intentional non-navigational episodic OLM in healthy adults.

Generally, studies were included in the review if a) they were peer-reviewed, b) their publication language was either English or German, and c) they included human participant groups with a mean age of 18 years and above. To identify brain regions involved in OLM, the reviewed studies had to include patients with focal brain lesions and control participants with healthy brains who completed intentional non-navigational episodic OLM tasks or healthy young adults who completed such tasks while brain activity was measured with fMRI or PET. For the characterization of changes in brain regions involved in OLM across adulthood, the reviewed studies had to examine brain activity with fMRI or PET while the same healthy adults completed intentional non-navigational episodic OLM tasks at different time points during their adulthood or when at least two groups of differentially aged healthy adults engaged in such tasks. For the portrayal of brain activation changes induced by cognitive training targeting OLM in healthy adults, the reviewed studies had to measure brain activity with fMRI or PET during the completion of an intentional non-navigational episodic OLM task in a group of healthy adults who had completed a cognitive training targeting this ability. The assessments had to take place at least before and after this training as well as at

the same time points in a group of healthy adults who did not complete such a training or took part in an alternative training targeting a different cognitive function.

To identify relevant studies, the databases PsycINFO, Web of Knowledge, Pubmed, and Medline were searched on the 30th of June 2013 with following keywords and combinations of keywords: *object-location memory, memory for object and location, memory for object-location(s), memory for objects and their locations, object(s) and location(s), object-location learning, spatial episodic memory, visuospatial associative memory, spatial context memory, spatial contextual memory, spatial location memory, object-location binding, binding item and location, spatial memory binding, associative binding, associative memory binding, memory binding, binding memory features, memory and binding, object-location association(s), object place association(s), what and where AND memory, object-location memory AND neural, object-location memory training, spatial memory training, associative memory training, object-location memory AND training, visuospatial memory AND training.*

3.3 Results

Search results

Initially, the literature search yielded 1193 hits. After eliminating 361 animal studies, 832 articles remained potentially eligible for review. From these, the following number of studies were additionally excluded: 99 studies presenting only behavioral data, 107 studies including only patient groups or presenting only behavioral data for different patient groups (clinical studies), 49 studies on motor tasks involving objects and locations, 198 studies on perception or attention for objects and their locations, 48 studies on memory for only objects or only locations, 67 studies on memory for words and their locations or for objects, their locations, and their order, 12 studies on auditory memory for objects and locations, 95 studies on working or short-term memory for objects and locations, 45 studies on memory for objects

and locations acquired by spatial navigation, 16 studies on incidental memory for objects and locations, and 72 studies on other subjects. From the reference lists of the remaining 24 relevant studies, seven additional suitable studies were found.

Among the finally 31 selected studies, 16 were lesion studies in which patients with focal brain lesions and control participants with healthy brains completed intentional non-navigational episodic OLM tasks, and 12 were fMRI and PET studies in which brain activity was measured while healthy young adults were engaged in such tasks. These studies were thus acceptable for the identification of brain regions involved in intentional non-navigational episodic OLM. Three other studies were fMRI or PET studies in which brain activity was assessed while a group of healthy young adults and a group of healthy older adults completed intentional non-navigational episodic OLM tasks. They were relevant for the characterization of changes in brain regions involved in this ability across adulthood. For the portrayal of brain activation changes induced by cognitive training targeting intentional non-navigational episodic OLM in healthy adults, no relevant studies were found. Figure 1 gives an overview about the selection process and the type of excluded and included studies.

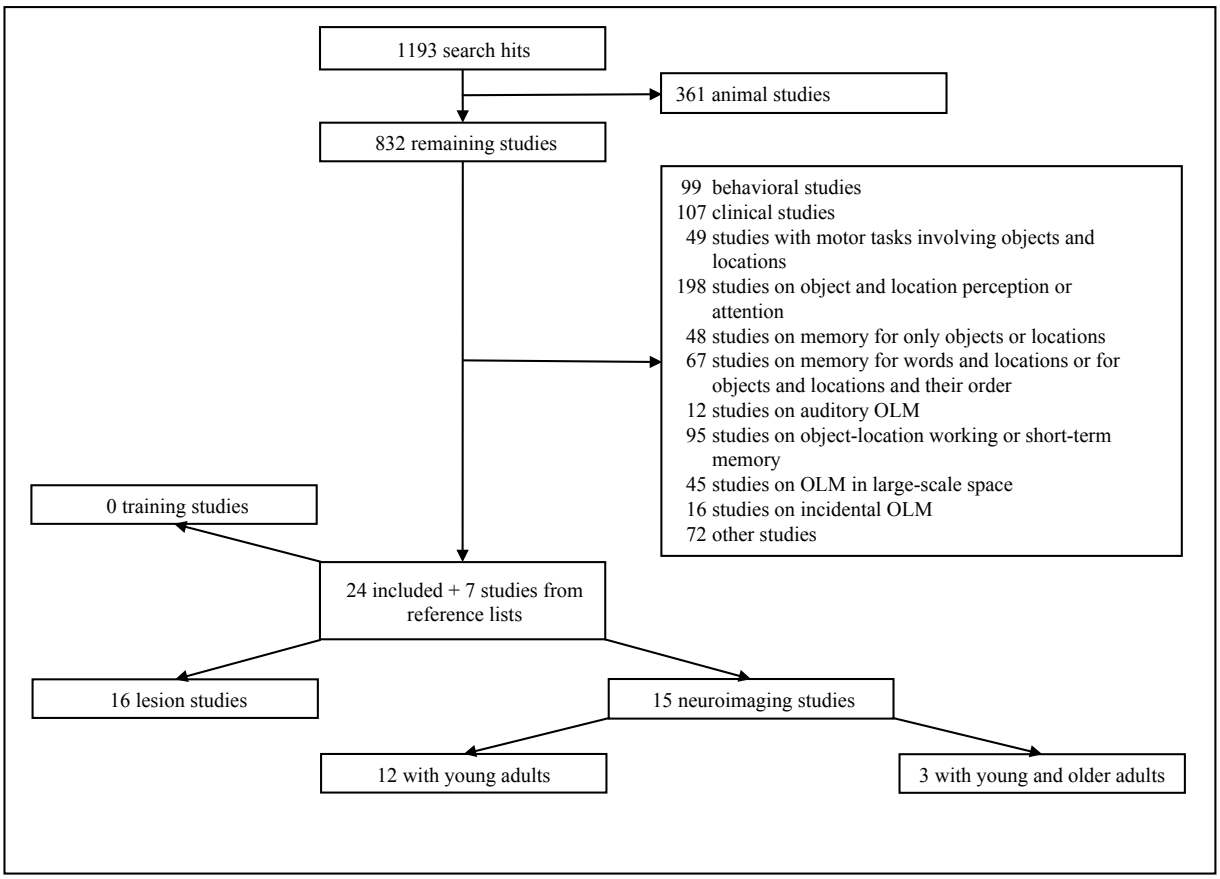

Figure 1. Inclusion procedure of reviewed studies.

Brain regions involved in intentional non-navigational episodic OLM

Evidence from lesion studies

In Table 1, characteristics of the patient and the control groups, the experimental and the possible control tasks as well as the results of the reviewed lesion studies in terms of performance differences between patient and control groups are described in detail. Following control tasks were taken into account throughout this review since they help to indicate which of the involved brain regions in OLM are probably dedicated to these subprocesses: object memory, location memory, and object-location perception. In addition, Table 1 indicates the type of relations between the locations of the objects in the experimental OLM tasks, which is categorical or coordinate.

Table 1. Reviewed lesion studies: Reference, patient and control groups, OLM and control task characteristics, OLM task type, and results

Reference	Patient groups	Control groups	OLM and control task characteristics	OLM task type	Results
Bohbot et al. (1998)	Lesion etiology: Unilateral thermo-coagulation along AMY-HC axis to alleviate pharmacologically intractable epilepsy, 4–17 years after operation, on antiepileptic drug therapy Inclusion criteria: Right-handedness, Wechsler-IQ > 74, no psychiatric disorder, no severe brain atrophy 4 groups: - 6 patients with lesions to RHC without lesions to the PHC (RTHC/-PHC) (age: *M* = 40.3, 38–42) - 4 patients with lesions to LHC without lesions to the PHC (LTHC/-PHC) (age: *M* = 44.5, 37–53) - 3 patients with lesions to RPHC with or without lesions to HC (RTPHC/±HC) (age: *M* = 40.3, 38–43) - 1 patient with lesions to LPHC without lesions to the HC (LTPHC/-HC) (age: 34) (most patients had additional unilateral temporal lesions)	8 patients with back pain (age: *M* = 41.4, 29–57)	**OLM tasks:** Encoding: Participants memorized the locations of four objects in a room viewing them from the door for 10 s Retrieval: 1) Immediate cued recall: Reconstruct locations of the objects in the room with object icons on a paper outline of the room. 2) Afterwards delayed associative recognition: Choose correct map out of four maps with four different spatial arrangements of the four encoded objects. 3) Afterwards delayed novelty-detection: Participants had to re-enter the room and correctly identify changes within 10 s (two objects had switched places, one object was displaced, and one object had remained at its previous location)	1) coordinate 2) categorical 3) categorical	**OLM tasks:** 1) RTPHC/±HC < C 2) All participants correctly completed the task except one RTHC/-PHC and one RTPHC/±HC patient 3) All participants correctly completed the task except one RTPHC/±HC patient
Bohbot et al. (2000)	Lesion etiology: Unilateral thermo-coagulation along AMY-HC axis to alleviate pharmacologically intractable epilepsy, 4–17 years after operation, on antiepileptic drug therapy Inclusion criteria: Right-handedness, Wechsler-IQ > 74, no psychiatric disorder, no severe brain atrophy 4 groups: - 7 patients with lesions to RHC without lesions to PHC (RTHC/-PHC) (age: *M* = 36.9, 29–49) - 4 patients with lesions to LHC without lesions to PHC (LTHC/-PHC) (age: *M* = 44.5, 37–53) - 5 patients with lesions to RPHC with or without lesions to HC (RTPHC/±HC) (age: *M* = 45.0, 38–59) - 1 patient with lesions to LPHC without lesions to HC (LTPHC/-HC) (age: 34) (most patients had additional unilateral temporal lesions) (same patient groups as in Bohbot et al. (1998) except 1 additional patient in the RTHC/-PHC group and 2 additional patients in the RTPHC/±HC group)	8 patients with back pain (age: *M* = 41.4, 29–57) (same as in Bohbot et al., 1998)	**OLM tasks:** Encoding: Participants memorized the locations of four objects in a room viewing them from the door for 10 s Retrieval: Immediate cued recall: Reconstruct locations of the objects in the room with object icons on a paper outline of the room **Control tasks:** *Object-location perception:* Pairs of displays of five spatially arranged objects were presented: 80% were identical, in 10% a new object appeared in the location of an original one, and in 10% two original objects switched their locations (object-location perception). Participants were instructed to indicate the object or object-location changes. No timing and trial number information was available	coordinate	**OLM tasks:** RTPHC/±HC < C **Control tasks :** Correct location change detection: RTPHC/±HC, RTHC/-PHC, LTHC/-PHC < C RTPHC/±HC < RTHC/-PHC
Crane & Milner (2005) Experiments 1 and 2	**Experiments 1 and 2** Lesion etiology: Unilateral anterior T lobectomy with excisions of most of the AMY, varying amounts of the HC, the parahippocampal gyrus, and the lateral neocortex with small HC excisions (< 1.5 cm of the anterior part; RThc or LThc), extensive HC excisions (> 1.5 cm of the anterior part; RTHC or LTHC), or	**Experiment 1** 14 healthy right-handed participants (age: *M* = 35, 16–54), no significant	**Experiment 1** **OLM tasks:** Encoding: Trial 1: An array of 12 toy objects on a plywood board had to be encoded within 60 s and each object named. Following trials: The array had to be encoded for 30 s without naming the objects	**Experiments 1 and 2** (tasks 1 and 2) coordinate	**Experiment 1** **OLM tasks**: Number of learning trials until perfect recall: RTHC > C (LThc, LTHC)

	selective unilateral AMY-HC-Ectomy (RAMYHC or LAMYHC) with removed AMY, the anterior 2–3 cm of the HC including the surrounding parahippocampal gyrus (the rest of the T neocortex was spared) to alleviate pharmacologically intractable epilepsy or to remove low-grade tumor, 3 months–29 years after operation Inclusion criteria: Left-sided speech representation demonstrated by preoperative intracarotid sodium amobarbital tests, Wechsler-IQ > 74, no structural damage outside lobe of resection **Experiment 1** 6 groups: - 7 RThc patients (age: *M* = 30, 16–54) - 8 RTHC patients (age: *M* = 34, 16–54) - 11 RAMYHC patients (age: *M* = 37, 16–54) - 5 LThc patients (age: *M* = 30, 15–45) - 11 LTHC patients (age: *M* = 36, 15–57) - 7 LAMYHC patients (age: *M* = 34, 21–46) **Experiment 2** 6 groups: - 8 RThc patients (age: *M* = 43, 33–53) - 18 RTHC patients (age: *M* = 35, 22–55) - 12 RAMYHC patients (age: *M* = 36, 21–48) - 11 LThc patients (age: *M* = 35, 19–48) - 11 LTHC patients (age: *M* = 37, 19–52) - 9 LAMYHC patients (age: *M* = 36, 22–44)	differences to patient groups in age and education **Experiment 2** 19 healthy right-handed participants (age: *M* = 35, 19–50), no significant differences to patient groups in age and education	Retrieval: All trials: Immediate cued recall: The array had to be reproduced with duplicate toy objects, no time restriction. Feedback was given on how many but not which objects had been correctly placed A maximum of 10 trials was conducted or so many trials until all 12 objects had been replaced correctly. The whole task was repeated after 3 min with a second array of 12 toy objects on a plywood board **Experiment 2** **OLM tasks:** 1) Encoding: An array of 12 toy objects on a plywood board had to be encoded within 60 s. The experimenter pointed to each object in turn for 5 s and each object had to be named. If it was not named within 5 s, the experimenter gave the name Retrieval: Delayed (filled 4 min) cued recall: The array had to be reproduced with duplicate toy objects, no time restriction 2) Same task as in Experiment 1, but only for one array **Control tasks:** *Object memory:* Immediately after encoding of OLM task 1, a surprise free recall test for the names of the encoded objects was given		RAMYHC > C (LThc) Immediate cued recall in trial 1: No significant group differences **Experiment 2** **OLM tasks:** 2) Number of learning trials until perfect recall: RTHC > C (LThc, LTHC, LAMYHC) RAMYHC > C Combined analysis of 1) and 2): ANOVA with group and type of recall (task 2 immediate cued recall in trial 1 vs. task 2 delayed cued recall) as factors: Main effect of group, no group x type of recall interaction: RTHC, RAMYHC < C (LTHC) **Control tasks:** No significant group differences
Grabowska et al. (1994)	Lesion etiology: Irreversible cooling of anterior part of the HC and/or the medial part of the AMY to alleviate pharmacologically intractable epilepsy - 7 right-handed patients (age: 35–41, Wechsler-IQ: 101–125) 3 groups: - 3 patients with lesion to BILAMY and LHC - 3 patients with lesions to RAMY and RHC - 1 patient with lesion only to RHC	11 healthy participants with no brain damage, matched as far as possible with patient group with respect to handedness, age, education, Wechsler-IQ (no data provided)	**OLM tasks:** Encoding: Nine geometrical shapes were presented simultaneously in 3x3-paper board grids for 18 s. Participants had to encode the locations of the shapes in the grid Retrieval: Immediate cued recall: Cards with encoded shapes had to be located in encoded locations in an empty 3x3-grid Encoding and retrieval of the shapes were repeated until perfect performances were reached in two consecutive trials	categorial	**OLM tasks:** Number of learning trials until criterion: Patients (AMY/HC) > C Patients with LHC = patients with RHC *M* percent of errors per trial: Patients (AMY/HC) > C Patients with LHC = patients with RHC
Holdstock et al. (2002)	Lesion etiology: Selective BILHC volume reduction after administration of an opiate drug for the relief of severe back pain which is thought to have resulted in an ischemic incident, 13 years post-event - 1 female patient (age: 61 for yes/no object recognition test, age: 59 for other tests, Wechsler-IQ: 102)	10 healthy female participants (age: *M* = 61.6, *SD* = 3.7 for the yes/no recognition test → 1 participant was replaced;	**OLM tasks:** Encoding in both tasks: Twelve pictures of nameable objects (half natural, half manmade) were arranged in predetermined positions on a white circular table. The participants' attention was directed to each object for 3 s and a natural/manmade decision for each object had to be made. The participants' attention was directed to each object a second time for 3 s to encode the locations of the objects Retrieval for both tasks was tested after a filled 40 s- and a filled 30 min-delay with a circle of cards and pictures of the objects. 1) Delayed associative recognition: The encoded location of	1) categorical 2) coordinate	**OLM tasks:** 1) Patient (BILHC) < C at both delays 2) Patient (BILHC) < C at both delays **Control tasks:** 1) Patient (BILHC) < C at both delays

		age: *M* = 58.8, *SD* = 3.8 for other tests)	each object had to be selected among four locations filled with this object of which three had been occupied by other objects during encoding. 2) Delayed cued recall: Pictures of the 12 encoded objects had to be placed in their encoded locations **Control tasks:** *Object memory:* Encoding in all tasks: Same as in OLM tasks Retrieval for all tasks was tested after a filled 40 s- and a filled 30 min-delay, except for task 3 in which retrieval was tested after filled 40 s only. 1) Delayed forced-recognition: The encoded object had to be selected from four presented objects (the encoded object and three very similar new ones). 2) Delayed free recall: The encoded objects had to be named. 3) Delayed yes/no recognition: The 12 encoded objects (four occurred twice, four occurred three times) were mixed with 36 new ones and presented subsequently to the participants. They had to indicate which had been encoded and which were new		2) No group differences at both delays 3) Patient (BILHC) < C
Kessels et al. (2000)	Lesion etiology: Unilateral neurosurgical removal of intracranial tumor Inclusion criteria: At least 1 year after operation, no radiotherapy -10 patients (age: *M* = 44.6, 19–65) Subgroups: - 1 patient with lesion in R posterior P - 1 patient with lesion in LP+O - 1 patient with lesion to R mid-P - 1 patient with RT lesion - 1 patient with L superior F lesion - 5 patients with LT or L basal F lesions	24 healthy participants (age: *M* = 50.7, *SD* = 7.8)	**OLM tasks:** Encoding in both tasks**:** Ten different objects at 10 different locations were presented simultaneously in an empty frame on a computer monitor and had to be encoded Retrieval: Cued recall immediately and after a delay of 3 min, no time restriction. 1) All encoded objects had to be reassigned to their encoded locations that were premarked by black dots. 2) All encoded objects had to be relocated to their encoded locations in an empty frame Two trials of 1) and 2) were conducted **Control tasks:** *1) Location memory (coordinate):* Encoding**:** Ten identical objects at 10 different locations were presented simultaneously in an empty frame on a computer monitor and had to be encoded Retrieval: Free recall immediately and after a delay of 3 min, no time restriction. Ten identical objects had to be relocated to their encoded locations in an empty frame *2) Object memory:* Encoding**:** Ten different objects were presented on a computer monitor and had to be encoded Retrieval: Immediate recognition: Encoded objects had to be identified among 20 objects (10 encoded and 10 new objects) *3) Object-location perception:* Copy a display of 10 different objects at different locations Two trials of 1), 2), and 3) were conducted	1) categorical 2) coordinate	**OLM tasks:** 1), 2) Immediate and delayed recall: Patient with lesion in R posterior P, patient with lesion in LP+O, patient with lesion to R mid-P < C **Control tasks** 1) Immediate and delayed recall: Patient with lesion in R posterior P, patient with RT lesion, patient with L superior F lesion < C 2) Patient with lesion in R posterior P, patient with lesion in LP+O, patient with lesion to R mid-P < C 3) Patient with lesion in R posterior P < C
Kessels et al. (2002)	Lesion etiology: Ischemic stroke, 5.2–92.8 months after stroke Inclusion criteria: Age between 25 and 75 years, no previous neurological or psychiatric disorder, at least 5 months after stroke, lesions visible on CT or MRI scans, no hemispatial neglect, no severe hemianopia - 50 patients (age: *M* = 52.4, 28–72) Subgroups (multiple lesions in patients possible): - 45 patients with cortical lesions (13 F, 18 T, 22 P, 18 O): patients with anterior (F and/or T) cortical	40 healthy participants (age: *M* = 52.3, 39–72), no significant group differences to patient groups in age, education level, and handedness	**OLM tasks:** Encoding in both tasks**:** Ten different objects at 10 different locations were presented simultaneously in an empty frame on a computer monitor for 30 s and had to be encoded Retrieval: Cued recall immediately and after an unfilled delay of 3 min, no time restriction. 1) All encoded objects had to be reassigned to their encoded locations that were premarked by black dots. 2) All encoded objects had to be relocated to their encoded locations in an empty frame Two trials of 1) and 2) were conducted	1) categorical 2) coordinate	**OLM tasks:** 1) Immediate recall: L < C R = BIL Cortical < C Posterior cortical, mixed cortical < C Delayed recall: L < C R = BIL Cortical < C Posterior cortical < C

	lesions, patients with posterior (P and/or O) cortical lesions, patients with mixed anterior and posterior cortical lesions (no exact participant number data available) - 5 patients with subcortical lesions → 28 patients with L, 16 with R, 6 with BIL lesions		**Control tasks:** *1) Location memory (coordinate):* Encoding**:** Ten identical objects at 10 different locations were presented simultaneously in an empty frame on a computer monitor for 30 s and had to be encoded Retrieval: Free recall immediately and after a delay of 3 min, no time restriction. Ten identical objects had to be relocated to their encoded locations in an empty frame *2) Object memory:* Encoding**:** Ten different objects were presented on a computer monitor for 30 s and had to be encoded Retrieval: Recognition immediately and after an unfilled 3-min delay: Encoded objects had to be identified among 20 objects (10 encoded and 10 new objects) *3) Object-location perception:* Copy a display of 10 different objects at different locations Two trials of 1), 2), and 3) were conducted		2) Immediate recall: L < C R = BIL Cortical < C Posterior cortical < C Delayed recall: L = R = BIL Cortical < C **Control tasks:** 1) Immediate recall: R < C L = BIL Cortical < C Anterior cortical = posterior cortical = mixed cortical Delayed recall: R < C L = BIL Cortical, subcortical < C Mixed cortical < C Anterior cortical = posterior cortical = mixed cortical 2) Sum of immediate and delayed recognition: R, BIL < C Anterior cortical = posterior cortical = mixed cortical 3) L, R < C Anterior cortical = posterior cortical = mixed cortical
Kessels et al. (2004)	Lesion etiology: Unilateral selective AMY-HC-Ectomy to alleviate pharmacologically intractable epilepsy caused by mesiotemporal sclerosis 2 groups: - 9 RAMYHC (age: *M* = 39.7, *SD* = 14.9) - 16 LAMYHC (age: *M* = 40.2, *SD* = 9.3)	30 healthy participants (age: *M* = 45.1, *SD* = 10.9), no significant differences to patient groups in age and gender, but slightly higher education level	**OLM tasks:** Encoding in both tasks**:** Ten different objects at 10 different locations were presented simultaneously on a computer monitor in an empty frame and had to be encoded for 30 s Retrieval: Immediate cued recall, no time restriction. 1) All encoded objects had to be reassigned to their encoded locations that were premarked by black dots. 2) All encoded objects had to be relocated to their encoded locations in an empty frame Two trials of 1) and 2) were conducted **Control tasks:** *Location memory:* Encoding in both tasks**:** Ten identical objects at 10 different locations were presented simultaneously on a computer monitor in an empty frame and had to be encoded. Retrieval: Immediate free recall, no time restriction. 1) Categorical: Ten identical objects had to be relocated to their encoded locations in a 7x7-grid superimposed on the previously empty frame. 2) Coordinate: Ten identical objects had to be relocated to their encoded locations in an empty frame Two trials of 1) and 2) were conducted	1) categorical 2) coordinate	**OLM tasks:** 1) No significant group differences 2) LAMYHC < C **Control tasks:** 1) No significant group differences 2) RAMYHC < C

King et al. (2002) Experiments 1 and 2	**Experiments 1 and 2** Lesion etiology: Selective BIL 50% reduction of HC volume with preserved surrounding tissue due to perinatal anoxia - 1 male patient (age: 25, Raven's IQ at age 22 = 90th percentile)	**Experiment 1** 12 healthy male participants (age: *M* = 20.9, 20–22, Raven's IQ: *M* = 86th percentile, *SD* = 8.0 %) **Experiment 2** 12 healthy male participants (age: *M* = 21.8, 19–26, Raven's IQ: *M* = 76.7th percentile, *SD* = 18.3%)	**Experiment 1** **OLM tasks:** Encoding: 10 objects were presented sequentially for 3 s (ISI = 1 s) randomly in 10 out of 21 placeholders on an otherwise empty computer screen Retrieval: Delayed forced-choice recognition after filled 5 s: Each object was presented at its original location and two other locations. Participants had to identify the encoded location of the objects. Four trials (four repetitions of the 10 object-location-probes) were conducted **Experiment 2** **OLM tasks:** 1) Encoding: In a 3D virtual reality environment, participants viewed an array of 21 randomly distributed placeholders located in a courtyard while looking down from two different vintage points. Seven or 10 objects were presented subsequently for 3 s (ISI = 1 s). Participants had to name the objects and encode their locations Retrieval: Delayed forced-choice recognition after filled 5 s: Each object was presented at its original location and two other locations. A) Egocentric, in the same view as during encoding or B) allocentric, in a shifted view (151º, 85º, or 66º rotation from the centroid of the placeholders). Participants had to identify the encoded location of the object. Four egocentric and eight allocentric trials were conducted. Ten objects were presented during encoding in egocentric and seven objects in allocentric trials 2) Same task as 1) except 4, 7, 10, or 13 objects were presented in A) egocentric trials and 1, 2, 3, 4, 5, or 7 objects in B) allocentric trials during encoding. For control participants, each object was presented at its original location and five other locations during retrieval. Only one type of view-shift (151º rotation from the centroid of the placeholders) was used during retrieval	**Experiment 1** categorical **Experiment 2** (tasks 1 and 2) categorical	**Experiment 1** **OLM tasks:** Patient (BILHC) < C **Experiment 2** 1) A) Patient (BILHC) < C B) Patient (BILHC) < C, impairment greater with larger viewpoint shift 2) A) 4, 7 objects: Patient (BILHC) = C 10, 13 objects: Patient (BILHC) < C B) 1 object: Patient (BILHC) = C 2–5, 7 objects: Patient (BILHC) < C
King et al. (2004) Experiments 2 and 3	**Experiments 2 and 3** Lesion etiology: Selective BIL 50% reduction of HC volume with preserved surrounding tissue due to perinatal anoxia - 1 male patient (age: 25, Raven's IQ = 120) (same participant as in King et al., 2002)	**Experiment 2** 13 healthy male participants (age: *M* = 23.8, *SD* = 3.2, Raven's IQ: *M* = 120.0, *SD* = 6.1) **Experiment 3** 14 healthy male participants (age: *M* = 21.7, *SD* = 2.4, Raven's IQ: *M* = 119.0, *SD* = 9.2)	**Experiment 2** **OLM tasks:** Encoding: In a 3D virtual reality environment, participants viewed an array of placeholders located in a small town square while looking down from the surrounding rooftops. Three objects were presented subsequently at random placeholders and participants had to encode their locations Retrieval: Delayed forced-choice recognition after filled 5 s: Each object was presented at its original location and at four other locations 1) Egocentric, in the same view as during encoding or 2) allocentric, in a shifted view (151º rotation from the centroid of the placeholders). Participants had to identify the encoded location of the object. In 1) the distractor locations were closer to the target and the encoded objects in locations farther from the viewing point than in 2) to achieve similar task difficulty for control participants. Four trials of 1) and 2) were conducted **Experiment 3** Encoding: In a 3D virtual reality environment, participants viewed an array of placeholders located in a small town square (different to Experiment 2) while looking down from the surrounding rooftops. Five objects were presented subsequently at random placeholders and participants had to encode their locations Retrieval: Delayed forced-choice recognition after filled 5 s: Each object was presented at its original location and at two other locations 1) Egocentric, in the same view as during encoding	**Experiments 2 and 3** 1) categorical 2) categorical	**Experiment 2** **OLM tasks:** 1) Patient (BILHC) > C 2) Patient (BILHC) < C **Experiment 3** Performance decrements: 1) - 2) Patient (BILHC) > C A) - B) Patient (BILHC) > C

			or 2) allocentric, in a shifted view (151º rotation from the centroid of the placeholders). In half of the egocentric and half of the allocentric trials, the objects were presented A) in the same town square as during encoding or B) in a different town square with the same placeholders. Participants had to identify the encoded locations of the objects. Eight trials of each condition were conducted		
Pigott & Milner (1993) Experiments 1 and 2	**Experiment 1** Lesion etiology: Unilateral partial F lobectomy or unilateral anterior T lobectomy including the anterior T neocortex, the AMY, and the uncus with small HC excisions (< 1.5 cm of the anterior part; RThc or LThc) or extensive HC excisions (> 1.5 cm of the anterior part including varying amounts of the surrounding parahippocampal gyrus; RTHC or LTHC) to alleviate pharmacologically intractable epilepsy, 2 weeks–26 years after operation Inclusion criteria: Left-sided speech representation demonstrated by preoperative intracarotid sodium amobarbital tests, Wechsler-IQ > 74 6 groups: - 12 RThc patients (age: *M* = 28.8, 16–39) - 13 RTHC patients (age: *M* = 30.5, 21–40) - 7 RF patients (age: *M* = 30.6, 21–49) - 14 LThc patients (age: *M* = 30.3, 19–43) - 14 LTHC patients (age: *M* = 26.8, 17–39) - 5 LF patients (age: *M* = 31.0, 23–40) **Experiment 2** Lesion etiology: Unilateral anterior T lobectomy to alleviate pharmacologically intractable epilepsy or in one patient an indolent tumor 2 groups: - 13 RT patients (age: *M* = 28.4, 17–38) - 14 LT patients (age: *M* = 33.1, 26–45) (5 RT and 4 LT patients had participated in Experiment 1)	**Experiment 1** 15 right-handed healthy participants (age: *M* = 27.7, 17–37) with no history of neurological illness or trauma to the central nervous system, no significant differences to patient groups in age and education **Experiment 2** 9 healthy participants (age: *M* = 26.0, 18–41), no significant differences to patient groups in age, Wechsler-IQ, and education	**Experiment 1** **OLM tasks:** Encoding: Ten target pictures of naturalistic scenes, each containing seven to 10 objects, had to be encoded. They were presented for 60 s with an ISI of 1 s Retrieval: Delayed associative recognition after 1 filled min: 100 test pictures were shown (each for 13 s, ISI = 1 s): Half of the test pictures were the same as the encoded scenes, half were transformed in five ways. Participants had to indicate if the test pictures were different from or the same as the encoded pictures, and if they were different, they were to report in what way. 1) Displacement transformation: One object was moved in the horizontal plane toward or away from the center. 2) Object-location transformation: Two objects of the same size and shape were interchanged **Control tasks:** *Object memory:* Encoding: Same as in OLM tasks Retrieval: Delayed recognition after 1 filled min: 1) Inventory transformation: One object was replaced by another of the same shape and size, but of a different type. 2) Figurative detail transformation: One object was replaced by another of the same shape, size, and type, but differed in details of appearance. 3) Deletion transformation: One object was removed from the scene **Experiment 2** **OLM tasks:** Same as in Experiment 1, only with immediate associative recognition **Control tasks:** *Object memory:* Same as in Experiment 1, only with immediate recognition	**Experiments 1 and 2** 1) coordinate 2) categorical	**Experiment 1** **OLM tasks:** 1) RThc, RTHC < C 2) RTHC < C (RF, LThc) **Control tasks:** 1) RThc, RTHC < C 2) RThc, RTHC < C (RF, LThc, LTHC, LF) 3) RThc, RTHC, LThc, LTHC < C (LF, RF excluded from analysis due to smaller variance) **Experiment 2** **OLM tasks:** 1), 2) No significant group differences **Control tasks:** 1), 2), 3) No significant group differences
Smith et al. (1995)	Lesion etiology: Unilateral cortical excisions of the anterior T lobes including the HC or of the F lobes to alleviate pharmacologically intractable epilepsy Inclusion criteria: Left-sided speech representation demonstrated by preoperative intracarotid sodium amobarbital tests, Wechsler-IQ > 74, no electrographic abnormality arising from both hemispheres, no fast growing tumors, no diffuse cerebral damage, younger than 51 years 4 groups: - 17 RT (+HC) patients (age: *M* = 30.9, 17–50) - 9 RF patients (age: *M* = 32.1, 22–44) - 24 LT (+HC) patients (age: *M* = 29.4, 13–47)	30 healthy participants (age: *M* = 28.0, 15–57), no significant differences to patient groups in age and education	**OLM tasks:** Three sets of 16 drawings of common objects were prepared and presented on sheets of paper Encoding: Condition 1), trial 1: Participants encoded the locations of the first set of 16 objects for 60 s. Trials 2 and 3: Participants encoded the same 16 objects of the first set in different locations for 60 s. Condition 2): Trials 1 and 2 same as in condition 1) but with another of the three sets of 16 objects. Trial 3: A different set of 16 objects was presented in different locations and participants had to encode the new object-location associations for 60 s Retrieval: For both conditions immediate cued recall: An empty sheet of paper of the size of the encoded spatial arrays divided into a 8x6-grid of squares of equal size was presented. Participants had to place cards of drawings of the encoded objects at the encoded locations A filled delay of 10 min was introduced between the two experimental conditions	coordinate	**OLM tasks:** MANOVA with group, condition, and trial as factors: No interaction of group with other factors, main effect of group, but post-hoc no significant differences between the participant groups Post-hoc analyses with one temporal group (T = LT + RT) and one frontal group (F = LF + RF): T, F < C Interference scores (*M* of trial 1 of both conditions - *M* of trials 2 and 3 of condition

	- 8 LF patients (age: *M* = 32.8, 21–45)				1 and trial 2 of condition 2): Analysis with T, F, and C groups: F > C
Stepankova et al. (2004)	Lesion etiology: Stereotaxic thermolesions involving medial T lobes to alleviate pharmacologically intractable epilepsy, 7–23 years after operation, all but one patient on antiepileptic drug therapy Inclusion criteria: Right-handedness, Wechsler-IQ > 74, no psychiatric disorder, no severe brain atrophy 2 groups: - 10 patients with lesions to RTHC (age: *M* = 43.7, 32–62) - 4 patients with lesions to LTHC (age: *M* = 47.3, 40–54) (most patients had additional T lesions) (7 RTHC and 4 LTHC patients same as in Bohbot et al., 1998)	9 healthy right-handed participants (age: *M* = 44.4, 32–56)	**OLM tasks:** Encoding: One to six common objects, each placed in one of 16 possible locations on the floor of a fully enclosed uniform circular arena, had to be encoded within 10 s while being viewed from the entrance of the arena Retrieval: 1) Immediate cued recall: The locations of the encoded objects in the arena had to be reconstructed on a paper map of the arena with photo icons of the objects. 2) Delayed cued recall after 1 filled min: All encoded objects were gathered in the middle of the arena and had to be replaced to their original locations. No time restriction was given in all retrieval conditions **Control tasks:** *Object-location perception:* On an empty paper map of the arena, the locations of the encoded objects in the arena had to be reconstructed with photo icons of the objects while viewing the object array in the arena from its entrance	1) coordinate 2) coordinate	**OLM tasks:** 1) RTHC < C 2) RTHC, LTHC < C **Control tasks :** No group differences
van Asselen et al. (2009)	Lesion etiology: Ischemic or hemorrhagic stroke Inclusion criteria: Age between 21 and 75 years, no other neurological or psychiatric illness, at least 6 months after stroke, at least one visible lesion on CT or MRI scans, no unilateral neglect, normal or corrected-to-normal vision 3 groups: - 22 R patients (age: *M* = 54.4, *SD* = 2.5) - 34 L patients (age: *M* = 54.8, *SD* = 2.3) - 5 BIL patients (age: *M* = 52.4, *SD* = 6.5)	77 healthy participants without a history of neurological or psychiatric illness (age: *M* = 54.4, *SD* = 1.1), no significant differences to patient groups in age, gender, and education level	**OLM tasks:** Encoding in both tasks**:** Ten different objects at 10 different locations were presented simultaneously in an empty frame on a computer monitor for 30 s and had to be encoded Retrieval: Immediate cued recall, no time restriction. 1) All encoded objects had to be reassigned to their encoded locations that were premarked by black dots. 2) All encoded objects had to be relocated to their encoded locations in an empty frame Two trials of 1) and 2) were conducted **Control tasks:** *1) Location memory (coordinate):* Encoding**:** Ten identical objects at 10 different locations were presented simultaneously in an empty frame on a computer monitor for 30 s and had to be encoded Retrieval: Immediate free recall, no time restriction. Ten identical objects had to be relocated to their encoded locations in an empty frame *2) Object memory:* Encoding**:** Ten different objects were presented on a computer monitor in a 2x5-grid for 30 s and had to be encoded Retrieval: Immediate recognition: Encoded objects had to be identified among 20 objects (10 encoded and 10 new objects) *3) Object-location perception:* Copy a display of 10 different objects at different locations Two trials of 1), 2), and 3) were conducted	1) categorical 2) coordinate	**OLM tasks:** 1) R, L, BIL < C 2) L, BIL < C **Control tasks:** 1) R < C 2) R, L, BIL < C 3) R, L, BIL < C
van Asselen et al. (2008)	Lesion etiology: Stroke Inclusion criteria: Age between 21 and 75 years, no other neurological or psychiatric illness, at least 6 months after stroke	36 healthy participants (age: *M* = 56.9, *SD* = 1.8), no significant differences to	**OLM tasks:** Encoding in both tasks**:** Ten different objects at 10 different locations were presented simultaneously in an empty frame on a computer monitor for 30 s and had to be encoded Retrieval: Immediate cued recall, no time restriction. 1) All encoded objects had to be	1) categorical 2) coordinate	**OLM tasks:** 1) No significant group differences 2) No significant group differences

	2 groups: - 12 R patients (age: *M* = 57.8, *SD* = 3.1) - 13 L patients (age: *M* = 57.8, *SD* = 2.8)	patient groups in age, gender, and education level	reassigned to their encoded locations that were premarked by black dots. 2) All encoded objects had to be relocated to their encoded locations in an empty frame Two trials of 1) and 2) were conducted **Control tasks:** *1) Location memory:* Encoding**:** Ten identical objects at 10 different locations were presented simultaneously on a computer monitor for 30 s and had to be encoded. Objects were presented A) categorical, in a visible 7x7-grid or B) coordinate, in an invisible 7x7-grid Retrieval: Immediate free recall, no time restriction. Ten identical objects had to be relocated to their encoded locations A) categorical, in a visible 7x7-grid or B) coordinate, in an invisible 7x7-grid *2) Object memory:* Encoding**:** Ten different objects were presented on a computer monitor in a 2x5-grid for 30 s and had to be encoded Retrieval: Immediate recognition: Encoded objects had to be identified among 20 objects (10 encoded and 10 new objects) *3) Object-location perception:* Copy a display of 10 different objects at different locations Two trials of 1), 2), and 3) were conducted		**Control tasks:** 1) A) L < C B) R < C 2) No significant group differences 3) R, L < C
Vargha-Kadem et al. (1997)	Lesion etiology: Selective BIL 50% reduction of HC volume with preserved surrounding tissue (except in third patient who also had a white matter reduction periventricular and in the corpus callosum) - 1 male patient (age: 19, verbal intelligence quotient (VIQ) = 109 at age 16, lesion due to perinatal anoxia, same as in King et al., 2002, 2004) - 1 female patient (age: 22, VIQ = 109 at age 19, lesion due to accidental intoxication with an asthma drug at age 9) - 1 female patient (age: 14, VIQ = 82 at 13, lesion due to heartbeat failure for 7–8 min after delivery)	11 healthy participants (age: 12–42, VIQ: *M* = 101.5, *SD* = 15.1)	**OLM tasks:** Encoding: In each trial, 20 different objects were presented subsequently on the right side of the computer screen. Each object was paired with a different circle in an irregular array of 40 circles located in the center of the computer screen. The paired circle was illuminated and the object appeared within it Retrieval: Immediate associative recognition: One previously lit circle was relit while two objects (the correct object and an object associated with another circle during encoding) were presented simultaneously on the right side of the screen. The correct object associated to the lit circle had to be touched. Performance feedback was given Trials were repeated until at least 18 correct choices were achieved in a trial or until 10 trials had been completed	categorical	**OLM tasks:** Number of learning trials until criterion: Patients (BILHC) > C Total errors across all conducted trials: Patients (BILHC) > C

Note: OLM = Object-location memory. C = Control group. L = Left hemisphere. R = Right hemisphere. BIL = Bilateral. F = Frontal. T = Temporal. P = Parietal. O = Occipital. hc = Lesions not extending anterior 1.5 cm of the hippocampus. HC = Lesions extending the anterior 1.5 cm of the hippocampus with or without affecting the surrounding parahippocampal gyrus or generally lesions affecting the hippocampus only. PHC = Parahippocampal cortex. AMY = Amygdala. Wechsler = WAIS-R: Wechsler Adult Intelligence Scale-Revised. Raven = Raven's Advanced Matrices. VIQ = Verbal Intelligence Quotient (subtest from WISC III: Wechsler Intelligence Scale for Children-Third Edition and WAIS-R).

The location, extent, and etiology of the patients' lesions and the interval between the occurrence of the lesions and study participation varied substantially across reviewed studies. In eight studies (Bohbot, Allen, & Nadel, 2000; Bohbot, Kalina, Stepankova, & Spackova, 1998; Crane & Milner, 2005; Grabowska, Luczywek, Fersten, Herman, & Szatkowska, 1994; Kessels, Hendriks, Schouten, van Asselen, & Postma, 2004; Pigott & Milner, 1993; Smith, Leonard, Crane, & Milner, 1995; Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004), patients had undergone surgery to treat pharmacologically intractable epilepsy and thus suffered from either unilateral frontal lesions or anterior and/or mediotemporal lesions which affected the amygdala, the hippocampus, and/or the surrounding parahippocampal gyrus to various extents. Two studies also included patients whom a tumor in anterior and/or mediotemporal brain regions was removed (Crane & Milner, 2005; Pigott & Milner, 1993 in experiment 2). Participants in these studies were tested two weeks to 29 years after the surgery. In three studies (Kessels, Kappelle, de Haan, & Postma, 2002; van Asselen et al., 2009; van Asselen, Kessels, Kappelle, & Postma, 2008), patients had brain lesions caused by an ischemic or hemorrhagic stroke. Patient groups in these studies were assessed at least five months after the incident. In the study by Kessels and colleagues (2000), patients had unilateral cortical lesions after having undergone neurosurgical removal of intracranial tumors at least one year before their participation in the study. Lesions were localized either in parietal and/or occipital or temporal and/or frontal brain regions. The four remaining studies included patients who had suffered a selective bilateral hippocampal volume reduction due to either an ischemic incident after the administration of an opiate drug for the relief of severe back pain (Holdstock et al. 2002), perinatal anoxia (King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002; King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004; Vargha-Kadem et al. 1997: same patient), incidental intoxication with an asthma drug, or heartbeat failure for several minutes after delivery (Vargha-Kadem et al., 1997). The first three studies

were single case studies, whereas the fourth study included three patients. Patients were tested 13–25 years after the occurrence of the brain damage.

Generally, besides lesion location, extent, and etiology, the reviewed studies differed considerably with regard to additional inclusion criteria for the patient groups. Kessels and colleagues (2004), Pigott and Milner (1993 in experiment 2), and the four case studies with patients with selective bilateral hippocampal volume reduction (Holdstock et al., 2002; King et al. 2002, 2004; Vargha-Kadem et al., 1997) did not require further inclusion criteria. Moreover, Kessels and colleagues (2000) only demanded their unilateral tumor patients to have had the tumor resection at least a year before their participation in the study, while Grabowska and colleagues (1994) merely required their patients to be right-handed. In the case of Kessels and colleagues (2000) and the four case studies with patients with selective bilateral hippocampal volume reductions, the lack of additional inclusion criteria is probably caused by the rareness of patients with such specific lesions. In all other studies, at least two of the following supplementary inclusion criteria were applied: no previous and/or current neurological and/or psychiatric disorders (Bohbot et al., 1998, 2000; Kessels et al., 2002; Stepankova et al., 2004; van Asselen et al., 2008, 2009), right-handedness (Bohbot et al., 1998, 2000; Stepankova et al., 2004) or left-sided speech representation demonstrated by preoperative intracarotid sodium amobarbital tests (Crane & Milner, 2005; Pigott & Milner, 1993 in experiment 1; Smith et al., 1995), a Wechsler-IQ greater than 74 points (Bohbot et al.,1998, 2000; Crane & Milner, 2005; Pigott & Milner, 1993 in experiment 1; Smith et al., 1995; Stepankova et al., 2004), no severe brain atrophy (Bohbot et al., 1998, 2000; Stepankova et al., 2004), no diffuse brain atrophy, no structural damage outside lobe of resection (Crane & Milner, 2005), no electrographic abnormality arising from both hemispheres nor fast growing tumors preoperatively (Smith et al., 1995), age 25–75 (Kessels et al., 2002; van Asselen et al., 2008, 2009) or younger than 51 years (Smith et al., 1995),

study participation five (Kessels et al., 2002) or six months after stroke (van Asselen et al., 2008, 2009), visibility of at least one lesion on computed tomography (CT) or MRI scans (Kessels et al., 2002; van Asselen et al., 2009), no neglect or severe hemianopia (Kessels et al. 2002; van Asselen et al., 2009), and normal or corrected-to-normal vision (van Asselen et al., 2009). Not taking into account the case studies with patients with selective bilateral hippocampal volume reductions, the sample sizes of the analyzed subgroups in all studies were rather small, often comprising less than 10 patients (range: 1–45).

Characteristics of control groups and inclusion criteria for these groups also varied substantially across reviewed studies. With the exception of Bohbot and colleagues (1998, 2000) who included patients with back pain as controls, all other studies' control groups comprised healthy participants. However, most studies did not report how the health status of control participants was determined. Just Pigott and Milner (1993) and van Asselen and colleagues (2009) reported that they had excluded participants with previous neurological disorders, and only in the latter study, participants with previous psychiatric disorders were banned from study participation. Moreover, many studies did not mention matching procedures between patient and control groups, nor did they report statistical data on group differences in important variables. If they did, the statistical analyses were conducted with the whole group of patients and not with the subgroups of patients and the control group, or they generally provided little data on the control group. Along these lines, Grabowska and colleagues (1994) merely provided the sample size of their control group, while Bohbot and colleagues (1998, 2000) and Kessels and colleagues (2000) only stated the number and age of their control participants. The four case studies with patients with selective bilateral hippocampal volume reductions did not provide statistical data on group differences between patients and control groups, but seemed to have closely matched their healthy control group to their respective participants in age (all studies), some measure of IQ (all studies but Holdstock

et al. 2002), and handedness (all studies except Vargha-Kadem et al., 1997, who did not provide information on handedness of their control group). In four of the eight remaining studies, patients and healthy control participants were right-handed or the patients had a left-sided speech representation according to a preoperative intracarotid sodium amobarbital test (Crane & Milner, 2005; Pigott & Milner, 1993 in experiment 1; Smith et al., 1995; Stepankova et al., 2004). Kessels and colleagues (2002) reported no significant statistical differences in handedness between their patients and healthy controls, whereas the four remaining studies did not provide data on the handedness of their participants (Kessels et al., 2004; Pigott & Milner, 1993 in experiment 2; van Asselen et al., 2008, 2009). In all eight studies, differences between the patient group as a whole and the healthy control group were statistically analyzed with regard to age and education. Kessels and colleagues (2004) and van Asselen and colleagues (2008, 2009) additionally tested for group differences in gender. With the exception of a slightly higher educational level of the healthy participants in the study by Kessels and colleagues (2004), there were no significant differences in these variables between the analyzed groups. Sample sizes of the control groups were larger than those of the patient subgroups and ranged from 8–77 participants across studies.

Material for OLM tasks included a varying number (1–20) of to-be-encoded object-location associations. Mainly computer paradigms were employed, but some studies also used paper-pencil tasks (Grabowska et al., 1994; Smith et al., 1995), presented real objects in a room (Bohbot et al., 1998, 2000), in a circular arena (Stepankova et al., 2004), on a circular table (Holdstock et al., 2002), or toy objects on a plywood board (Crane & Milner, 2005). Most computer paradigms were two-dimensional. Only King and colleagues (2002, 2004) presented the object-location associations in a three-dimensional virtual reality environment. Besides Grabowska and colleagues (1994) who used geometrical shapes as objects, all other studies applied nameable everyday objects in their OLM tasks. The object-location

associations were mainly presented in grids or empty frames, seldom they were embedded in naturalistic scenes (King et al., 2002, 2004; Pigott & Milner, 1993). Only in one task (King et al., 2004), participants saw the object-location associations in different background environments during encoding and retrieval, thereby prohibiting the use of background characteristics as retrieval cues. In two studies (King et al. 2002, 2004), but altogether in four OLM tasks, the object-location associations were presented in different views during encoding and retrieval, thus clearly posing higher demands on allocentric location processing. All other OLM tasks could be solved in egocentric manner. However, they probably also induced allocentric location processing, since participants most certainly used the borders of the computer screen, room, table, or arena as well as the characteristics of the grids and naturalistic scenes as body-independent spatial cues.

Three studies included indirect OLM encoding measures (number of learning trials until criterion, total errors across all or mean error percentage per learning trial). In two of them (Grabowska et al., 1994; Vargha-Kadem et al., 1997), relations between the locations of the objects were categorical, and in one (Crane & Milner, 2005) they were coordinate in two separately conducted experiments. Vargha-Kadem and colleagues (1997) tested retrieval with immediate associative recognition, while it was assessed with immediate cued recall in the other two studies. Furthermore, participants of three studies (Crane & Milner, 2005; King et al., 2002, 2004) were asked to name the objects during encoding, whereas in one study (Holdstock et al., 2002) participants had to decide whether the objects were natural or manmade.

All other studies focused on retrieval processes. Ten studies investigated immediate cued OLM recall (Bohbot et al., 1998, 2000; Crane & Milner, 2005; Kessels et al., 2000, 2002, 2004; Smith et al., 1995; Stepankova et al., 2004; van Asselen et al., 2008, 2009) and five studies (Crane & Milner, 2005; Holdstock et al., 2002; Kessels et al., 2000, 2002;

Stepankova et al., 2004) delayed cued OLM recall. In one study (Stepankova et al., 2004), relations between the locations of the objects were categorical. Three studies (Kessels et al., 2000, 2002, 2004) included both a categorical and a coordinate OLM task. In all other studies, the immediate or delayed cued OLM recall tasks demanded coordinate location processing. One study implemented an immediate OLM recognition task (Pigott & Milner, 1993), whereas five studies assessed delayed OLM recognition (Bohbot et al., 1998; Holdstock et al., 2002; King et al., 2002, 2004; Pigott & Milner, 1993). In all OLM recognition studies, relations between the locations of the objects were categorical.

The use of control tasks also varied across studies. Six studies (Bohbot et al., 1998; Grabowska et al., 1994; King et al., 2002, 2004; Smith et al., 1995; Vargha-Kadem et al., 1997) did not implement any control tasks. Seven studies (Crane & Milner, 2005; Holdstock et al., 2002; Kessels et al., 2000; Pigott & Milner, 1993; van Asselen et al., 2008, 2009) included object memory tasks, five studies (Kessels et al., 2000, 2002, 2004; van Asselen et al., 2008, 2009) location memory tasks, and six studies (Bohbot et al., 2000; Kessels et al., 2000, 2002; Stepankova et al., 2004; van Asselen et al., 2008, 2009) object-location perception control tasks. The employed control tasks were equal in terms of material and structure to OLM tasks when assessing object or location memory, although often different retrieval types (free recall in all location memory tasks, free recall or recognition in object memory tasks) were implemented instead (Crane & Milner, 2005; Kessels et al., 2000, 2002, 2004; van Asselen et al., 2008, 2009) or additionally (Holdstock et al., 2002). All five studies implementing location memory control tasks matched these with regard to the spatial relations between the objects' locations to an experimental coordinate OLM task, but only two studies (Kessels et al., 2004; van Asselen et al., 2008) additionally presented them matched with regard to the spatial relations between the objects' locations to a further assessed experimental categorical OLM task. All object-location perception control tasks involved the copying of

similar materials as used in the OLM tasks with the exception of one study (Bohbot et al., 2000) in which the object-location perception task was very different from the OLM task with respect to material and procedure.

Three of the reviewed lesion studies (Kessels et al., 2002; van Asselen et al., 2008, 2009) focused on the lateralization of OLM and related subprocesses (location memory, object memory, and object-location perception). All three studies included patients after stroke with lesions either to the left or the right hemisphere. In two studies (Kessels et al., 2002; van Asselen et al., 2009), also a small group of stroke patients with bilateral lesions was assessed. The same computer paradigm was applied in all three studies which measured immediate cued coordinate and categorical OLM recall and incorporated also following closely matched control tasks: immediate free coordinate location recall, immediate object recognition, and object-location perception (copying an array of objects at different locations). In addition, van Asselen and colleagues (2008) used a closely matched task for immediate free categorical location recall. Kessels and colleagues (2002) also tested delayed (3 min) cued recall for coordinate and categorical OLM, free coordinate location recall, and object recognition, but with regard to the latter solely employed a combined measure for immediate and delayed object recognition.

In two of the three studies (Kessels et al., 2002; van Asselen et al., 2009), only patients with left-sided brain lesions (in the latter study also patients with bilateral brain lesions) were impaired in immediate cued coordinate OLM recall, while van Asselen and colleagues (2008) found no performance differences between their patient groups and their healthy control group. Along these lines, Kessels and colleagues (2002) reported similar performances for both patient groups and the healthy participants in delayed cued coordinate OLM recall. Overall, there seems to be some indication of a left-lateralization of coordinate OLM. However, the findings on immediate cued categorical OLM recall varied greatly between the

three studies, thus hindering firm conclusions: From no significant performance differences to healthy controls (van Asselen et al., 2008) over performance decrements for patients with left-sided brain lesions only (Kessels et al., 2002) to impairments for patients with left- and right-sided as well as bilateral brain lesions (van Asselen et al., 2009). For delayed cued categorical OLM recall, Kessels and colleagues (2002) found only performance impairments in their patient group with lesions to the left hemisphere.

In contrast to the above findings supporting a left-lateralization of coordinate OLM, the three studies demonstrated a right-lateralization of coordinate location memory. In all studies, only patients with right-sided brain lesions performed worse than the healthy control groups in immediate free coordinate location recall. In addition, Kessels and colleagues (2002) found only patients with right-sided brain lesions to be impaired in delayed free coordinate location recall compared to healthy participants. For immediate free categorical location recall, van Asselen and colleagues (2009) demonstrated that patients with left-sided brain lesions performed worse than healthy participants, which points to a left lateralization for categorical location memory. For immediate and delayed object recognition, the findings differed again greatly between the three studies, consequently allowing no general conclusions: From no performance differences between patient groups and healthy controls (van Asselen et al., 2008) over performance decrements for patients with right-sided and bilateral brain lesions (Kessels et al., 2002) to impairments for patients with left- and right-sided as well as bilateral brain lesions (van Asselen et al., 2009). In contrast, patients with left- and right-sided brain lesions in all three studies – and in the study by van Asselen and colleagues (2009) also patients with bilateral brain lesions – performed worse than the healthy control groups in object-location perception. Therefore, brain regions of both hemispheres seem to play a role in object-location perception.

Kessels and colleagues (2002) divided their stroke patients into a group with cortical lesions and a group with subcortical lesions, the latter including only five patients. For all assessed OLM tasks (immediate and delayed cued categorical and coordinate recall), only patients with cortical lesions were impaired in comparison to the healthy participants, suggesting that subcortical brain regions are not involved in both coordinate and categorical OLM. For immediate free coordinate location recall, only patients with cortical lesions performed worse than the control groups, but for delayed free coordinate location recall also patients with subcortical lesions were impaired, pointing to some involvement of subcortical brain regions in coordinate location memory. There were no significant performance differences between patient groups and healthy participants for immediate and delayed object recognition and object-location perception.

In another step, Kessels and colleagues (2002) divided their patients with cortical lesions into three further subgroups: patients with anterior (frontal and temporal), patients with posterior (parietal and occipital), and patients with mixed anterior and posterior cortical lesions. For immediate cued coordinate OLM recall, only patients with posterior cortical lesions performed worse than healthy participants, but there were no significant performance differences between the patient groups and the healthy controls for delayed cued coordinate OLM recall. In contrast, for immediate cued categorical OLM recall, patients with posterior as well as patients with mixed anterior and posterior cortical lesions showed performance decrements in comparison to the healthy control group. In delayed cued categorical OLM recall, only patients with posterior cortical lesions were impaired. There were no significant performance differences between the experimental groups for immediate free coordinate location recall, immediate and delayed object recognition, and object-location perception. However, only the patients with mixed anterior and posterior cortical lesions performed worse than the healthy participants in delayed free coordinate location recall. Overall, these findings

suggest a greater involvement of parietal and occipital than frontal and temporal brain regions in both coordinate and categorical OLM. There is some indication of an additional contribution of frontal and temporal brain regions in immediate cued categorical OLM recall, while none of these brain regions seem to play a specific role for coordinate location memory, object memory, or object-location perception.

Kessels and colleagues (2000) used the same paradigm as Kessels and colleagues (2002) (with the exception of delayed object recognition) in 10 patients with cortical lesions after neurosurgical removal of unilateral intracranial tumors and 24 healthy control participants. Three patients – one with a lesion to the right posterior parietal cortex, one with lesions affecting both left parietal and occipital lobes, and one with a right mid-parietal lesion – performed worse than the healthy control group in immediate and delayed cued coordinate and categorical OLM recall. The seven patients who performed as well as the healthy participants had only unilateral left- or right-sided frontal and/or temporal lesions. Similarly to the findings by Kessels and colleagues (2002), this points to an important role of parietal and occipital brain regions in both coordinate and categorical OLM, whereas frontal and temporal brain regions do not appear to be involved. All three patients with OLM impairments also performed worse than the healthy control group in immediate object recognition. Since object memory is a subprocess of OLM, bilateral parietal and left occipital regions seem to be specialized for object memory rather than for OLM per se. Moreover, the patient with the lesion to the right posterior parietal cortex was the only patient who was impaired in object-location perception, indicating that the right posterior parietal cortex could be essential for this ability. In line with this conclusion, the patient was also impaired in immediate and delayed free coordinate location recall, i.e., his/her object-location perception deficit affected all memory tasks involving objects, locations, and object-location associations. Besides this patient, two patients – one with a lesion to the right temporal cortex

and one with a lesion to the left superior frontal cortex – were impaired in both immediate and delayed free coordinate location recall, suggesting an involvement of these two brain regions in coordinate location memory. However, this contrasts the findings from the three lateralization studies (Kessels at al., 2002; van Asselen et al., 2008, 2009) which indicated a lateralization to the right hemisphere for immediate and delayed free coordinate location recall.

Two further studies (Pigott & Milner, 1993; Smith et al., 1995) specifically explored the involvement of temporal and frontal brain regions in OLM. Both studies included patients who had undergone unilateral anterior and/or mediotemporal or frontal excisions in order to alleviate pharmacologically intractable epilepsy. Smith and colleagues (1993) assessed patients with left- or right-sided frontal lesions, patients with left- or right-sided anterior and/or mediotemporal lesions, and healthy control participants for immediate cued coordinate OLM with a paper-pencil task including two conditions: one imposing high interference (in three trials different locations of the same 16 objects had to be encoded) and one imposing less interference (only in the first two trials the locations of the same 16 objects had to be encoded, whereas in trial 3 the locations of 16 new objects had to be memorized). A multivariate analysis of variance (MANOVA) with group as between-subject factor and condition and trial as within-subject factors revealed a main effect of group, but no interaction of group with the other two factors. Post-hoc comparisons between the experimental groups were not significant. Therefore, the original four patient groups were pooled into two new groups: one with patients with temporal lesions and one with patients with frontal lesions. Both patient groups were impaired in comparison to the healthy participants in an OLM measure including data across all conditions and trials but did not differ from each other, suggesting – in contrast to the findings by Kessels and colleagues (2000, 2002) – that both temporal and frontal regions are important for immediate cued coordinate OLM recall. Smith

and colleagues (1995) also compared the three new experimental groups on an interference score (difference between the mean of the performances in the first trials of both conditions and the mean of the performances in the trials of both conditions in which the same objects as in the previous trials had to be encoded). Only the patients with frontal lesions were more susceptible to interference than the healthy participants. Thus, their performance decrements in the general coordinate OLM measure may be due to their greater sensitivity to interference rather than to an impairment of coordinate OLM per se. This suggestion is supported by the findings by Pigott and Milner (1993) who examined delayed (1 min) associative coordinate and categorical OLM recognition and three types of delayed (1 min) object recognition with a computer paradigm in two groups of patients with right-sided and two groups of patients with left-sided anterior and/or mediotemporal lesions, in patients with left- or right-sided frontal lesions as well as in healthy control participants. Only patients with some form of temporal lesion performed worse than the healthy participants in the experimental tasks.

Six further studies included patient groups that had undergone surgery leading to the removal of or to neuron death in anterior and/or medial temporal regions in order to alleviate pharmacologically intractable epilepsy. In addition, Pigott and Milner (1993) reported the results of a second experiment in which they included only patients with such lesions. In four studies (Bohbot et al., 1998, 2000; Pigott & Milner, 1993; Stepankova et al., 2004), the surgery had involved varying amounts of the amygdala, the hippocampus, the parahippocampal gyrus, and/or other anterior or mediotemporal regions, in two studies (Grabowska et al., 1994; Kessels et al., 2004), varying amounts of the amygdala and the hippocampus had been affected, and in one study (Crane & Milner, 2005), patient groups with both types of surgical results were included.

Pigott and Milner (1993 in experiment 2) did not find significant performance differences in immediate associative coordinate and categorical OLM recognition as well as

in three immediate object recognition tasks assessed with a computer paradigm between patients with left-sided anterior and/or mediotemporal lesions, patients with right-sided anterior and/or mediotemporal lesions, and healthy participants. However, Stepankova and colleagues (2004) demonstrated that patients with right-sided anterior and/or mediotemporal lesions including the right hippocampus (although two of the 10 patients had also bilateral damage to the amygdala) were impaired compared to healthy control participants in immediate and delayed cued coordinate recall of the locations of six real objects in a circular arena. In contrast, patients with left-sided anterior and/or mediotemporal lesions including the left hippocampus (although one of the four patients had also bilateral damage to the amygdala) performed worse than the healthy control group only in delayed cued coordinate recall of these object-location associations. There were no performance differences between the two patient groups and the control group in a closely matched object-location perception task, suggesting that bilateral anterior and medial temporal brain regions – particularly the hippocampus – are specifically involved in coordinate OLM. In contrast, Kessels and colleagues (2004) found that patients with selective lesions to the left amygdala and/or the left hippocampus performed worse than healthy controls in immediate cued coordinate OLM recall, whereas patients with selective lesions to the right amygdala and/or the right hippocampus were impaired only in immediate free coordinate location recall, indicating a specific role of the left amygdala and/or the left hippocampus in coordinate OLM.

In addition, Kessels and colleagues (2004) reported no performance differences between the three experimental groups in immediate cued categorical OLM recall and immediate free categorical location recall. These results imply that neither the hippocampus nor the amygdala of both hemispheres are involved in categorical OLM. On the other hand, Grabowska and colleagues (1994) demonstrated that patients with lesions either to the left hippocampus and the bilateral amygdala, the right hippocampus and the right amygdala, or only the right

hippocampus were impaired compared to healthy participants in two categorical OLM encoding measures (number of learning trials until perfect immediate cued performance, mean error percentage per trial across all learning trials) assessed with a paper-pencil task. In addition, there were no performance differences between patients with lesions to the left and patients with lesions to the right hippocampus, demonstrating that neither the hippocampus nor the amygdala of both hemispheres are important for categorical OLM or at least for categorical OLM encoding. However, this conclusion is limited by the very small size of the subsamples of patients with left- or right-sided hippocampal lesions (only three and four patients, respectively).

Bohbot and colleagues (1998, 2000) more specifically investigated the respective roles of the hippocampus and the parahippocampal cortex in OLM. Both studies included almost the same sample of patients with unilateral anterior and/or mediotemporal lesions either comprising the hippocampus but not the parahippocampal cortex or the parahippocampal cortex with or without additional lesions also to the hippocampus. In both studies, only one patient with a lesion affecting the left parahippocampal cortex (and not the left hippocampus) was included and one of the patients with a lesion to the right hippocampus had also bilateral damage to the amygdala. Overall, only patients with lesions to the right parahippocampal cortex with or without an additional lesion to the right hippocampus performed worse than the control group in immediate cued coordinate recall for the locations of four real objects in a room, indicating a greater importance of the right parahippocampal cortex than the right hippocampus in coordinate OLM. Bohbot and colleagues (1998) also assessed two types of delayed categorical OLM recognition. These tasks proved to be too easy since all participants besides one or two patients were able to reach perfect performance in these tasks.

Bohbot and colleagues (2000) included a computerized object-perception control task instead (recognition of location switches of two objects in pairs of displays with five spatially

arranged objects). In contrast to Stepankova and colleagues (2004) who did not find object-location perception differences between the patients with left- or right-sided anterior and/or mediotemporal lesions involving the hippocampus and the healthy participants, the patients with lesions to the right parahippocampal cortex with or without an additional lesion to the right hippocampus, patients with a lesion to the right hippocampus but not to the right parahippocampal cortex as well as the one patient with the lesion to the left parahippocampal cortex but not to the left hippocampus performed worse than the control group in this object-location perception task. In addition, the patients with lesions to the right parahippocampal cortex with or without an additional lesion to the right hippocampus showed performance decrements in comparison to the patients with a lesion to the right hippocampus but not to the right parahippocampal cortex. This indicates that the right parahippocampal cortex may be particularly important for object-location perception, but also that the left parahippocampal cortex and the right hippocampus appear to be involved in this ability. Although the findings with regard to object-location perception contradict those of Stepankova and colleagues (2004), they may be explained by the fact that only three of their 10 patients with right-sided temporal lesions and none of their four patients with left-sided temporal regions had damage to the parahippocampal cortex or by the very different type of object-location perception task used by Bohbot and colleagues (2000). However, they also suggest that the specific coordinate OLM deficit of the patients with lesions to the right parahippocampal cortex with or without an additional lesion to the right hippocampus may be a consequence of their strong deficit in object-location perception.

In their first experiment, Pigott and Milner (1993) assessed two groups of patients with either left- or right-sided anterior and/or mediotemporal lesions. The two respective groups differed in terms of the extent of surgical removal of hippocampal and/or parahippocampal gyrus. In the first group, only the most anterior part (< 1.5 cm) of the hippocampus had been

removed, whereas in the second group the lesion extended beyond the anterior 1.5 cm of the hippocampus and could also involve the surrounding parahippocampal gyrus. The authors found that both patient groups with right-sided temporal lesions performed worse than the healthy participants in their computerized delayed (1 min) associative coordinate and categorical OLM recognition tasks. Yet, there were no performance differences between the patient groups with left-sided temporal lesions and the healthy control group as well as between the two groups with right-sided temporal lesions. Contrary to the findings by Bohbot and colleagues (2000), these results speak for a particular involvement of the anterior part of the right hippocampus and not the right parahippocampal gyrus in coordinate and categorical OLM. However, both patient groups with right-sided temporal lesions were also impaired in three delayed object recognition control tasks (in one task also both groups with left-sided temporal lesions), indicating that within OLM the right hippocampus may strongly support object memory and the right parahippocampal gyrus object-location perception.

Finally, Crane and Milner (2005) assessed coordinate OLM in six groups of patients with lesions to varying amounts of anterior and mediotemporal brain regions. Four groups were similar to the ones investigated by Pigott and Milner (1993). The additional two groups comprised patients with either left- or right-sided unilateral lesions affecting the amygdala, the anterior 2-3 cm of the hippocampus including the parahippocampal gyrus. Two experiments were conducted. In both experiments, encoding (number of learning trials until perfect performance) and immediate cued recall (in the first trial) of the locations of 12 toy objects on a plywood board were measured. In the second experiment, a similar OLM task with only one encoding and one delayed (4 min) cued recall trial and a closely matched free object recall control task were additionally employed. In both experiments, only the group with right-sided lesions to anterior and/or mediotemporal brain regions affecting an extended part of the hippocampus and/or the surrounding parahippocampal gyrus and the group with

selective lesions to the right amygdala and the right hippocampus including the parahippocampal gyrus were impaired in comparison to the healthy controls in coordinate OLM encoding, however, they did not differ from each other. In addition, there were no performance differences between the experimental groups for immediate cued coordinate OLM recall in the first experiment. In the second experiment, an analysis of variance (ANOVA) with the factors experimental group and type of OLM recall (immediate cued recall in task 1, delayed cued recall in task 2) revealed a main effect of group, but no interaction between group and type of OLM recall. Again, only the group with right-sided lesions to anterior and/or mediotemporal brain regions affecting an extended part of the hippocampus and/or the surrounding parahippocampal gyrus and the group with selective lesions to the right amygdala and the right hippocampus including the parahippocampal gyrus performed worse than the healthy controls. Once more, the two groups did not differ from each other. There were also no significant group differences in free immediate object recall. Consequently, these findings partly contradict those by Pigott and Milner (1993), demonstrating that extended lesions to the right hippocampus and the surrounding parahippocampal gyrus are affecting coordinate OLM and not only its subprocess, i.e., object memory. In fact, the more anterior part of the right hippocampus and the surrounding parahippocampal gyrus may be critical for coordinate OLM and object recognition, whereas the more posterior part might be essential for cued immediate and delayed coordinate OLM recall.

The four last studies were case studies of patients with selective bilateral hippocampal lesions. Vharga-Kadem and colleagues (1997) demonstrated that the three patients with selective bilateral hippocampal lesions were impaired in contrast to a group of healthy participants in two measures of associative categorical OLM (number of learning trials until 18 of 20 encoded objects were allocated to their correct locations, total errors across all

learning trials). Holdstock and colleagues (2002) found that the patient with bilateral hippocampal lesions performed worse than the healthy control participants in delayed (40 s and 30 min) associative categorical recognition and delayed (40 s and 30 min) coordinate cued recall of the locations of 12 objects on a circular table. However, the patient was also impaired in comparison to the healthy control group in three out of five closely matched measures of delayed object memory (impaired in three recognition, but not in two free recall measures).

King and colleagues (2002, 2004) tested in two studies the bilateral involvement of the hippocampus in different categorical OLM tasks. In their first study, the patient was impaired in comparison to the healthy control participants in three computerized tasks assessing delayed (5 s) OLM recognition. One task tested categorical OLM in a 2D environment, whereas the two other tasks assessed OLM in a 3D virtual reality environment. Both latter tasks included a condition in which the objects were presented using the same viewpoint during encoding and retrieval and therefore allowing for egocentric location processing and a condition in which the objects were shown from different views during encoding and retrieval, thus demanding allocentric location processing. In one of the 3D tasks, objects were shown from three different views, in the other tasks different numbers of object-location associations had to be encoded. The patient with selective bilateral hippocampal lesions was impaired in both egocentric and allocentric conditions of the two 3D tasks, but the impairment was more pronounced in the allocentric condition (observed with a smaller number of object-location associations and increased with the size of the viewpoint shift). In their second study, King and colleagues (2004) confirmed their former findings, demonstrating with very similar versions of their previously 3D delayed categorical OLM recognition paradigm that the same patient performed worse than the healthy participants in the allocentric condition of the paradigm. Furthermore, the patient was especially impaired in an additional version of the

task in which the appearance of the virtual environment was changed from encoding to retrieval, however the spatial arrangement of the locations of the encoded objects remained the same. Concluding, the four studies with one to three patients with selective bilateral hippocampal lesions demonstrated that the hippocampus of both hemispheres seems to be involved in categorical OLM recognition, that is in both encoding and delayed retrieval, particularly when allocentric location processing is required and characteristics of the background environment cannot be used as spatial retrieval cues, but that the same structures may also be critical for object memory.

Overall, the reviewed lesion studies point to the specific involvement of the right hippocampus, the right amygdala, and the right parahipppocampal gyrus in coordinate OLM with the restriction that some studies (all using the same computer paradigm) only found regions of the left hemisphere to be involved. Other anterior or mediotemporal brain regions may also play a role. In addition, bilateral parietal and occipital regions seem to be important for coordinate OLM, whereas the frontal lobes appear to be only involved when coordinate OLM tasks elicit high proactive interference. Moreover, coordinate OLM does not seem to depend on subcortical regions. Among the regions involved in OLM, the right posterior parietal cortex and the right parahippocampal gyrus – in particular the parahippocampal cortex – may be especially important for object-location perception, whereas bilateral parietal areas and left occipital regions may support object memory and the right hippocampus all kinds of memory processes involved in OLM (object memory, location memory, object-location binding). In addition, there is some indication that the left superior frontal gyrus is involved in coordinate location memory. Categorical OLM has been less thoroughly investigated than coordinate OLM. Generally, the findings point to the involvement of similar regions in categorical and coordinate OLM. However, they less clearly support the right-

lateralization of implicated anterior and mediotemporal regions and additionally emphasize the bilateral involvement of the hippocampus in allocentric OLM.

Evidence from neuroimaging studies with healthy young adults

In Table 2, characteristics of participants, features of the encoding, delay, and retrieval phases of the experimental OLM task and of possible control tasks as well as the results in terms of OLM specific brain regions of the reviewed neuroimaging studies with healthy young adults are described in detail.

Six studies (Büchel, Coull, & Friston, 1999; Cansino et al., 2002; de Rover et al., 2008; Hales & Brewer, 2013; Sommer et al., 2005a, b) employed fMRI and six studies (Johnsrude, et al., 1999; Köhler, McIntosh, Moscovitch, & Winocur, 1998a; Köhler, Moscovitch, Winocur, Houle, & McIntosh, 1998b; Moscovitch, Kapur, Köhler, & Houle, 1995; Owen, Milner, Petrides, & Evans, 1996a; Owen et al., 1996b) PET to measure brain activity during OLM and/or control tasks. Cansino and colleagues (2002) and de Rover and colleagues (2008) investigated OLM specific brain activity during retrieval, whereas all other fMRI studies focused on encoding only. In other words, the study by Cansino and colleagues (2002) was the only one that analyzed brain activity during OLM encoding and retrieval. In contrast, all PET studies explored OLM specific brain activity during retrieval. Merely Owen and colleagues (1996a, b) also investigated OLM encoding.

Table 2. Reviewed functional neuroimaging studies with young adults: Reference, neuroimaging method, participants, OLM and control task characteristics, and results

Reference	Neuro-imaging method	Participants	Task characteristics			Results
			Encoding	Delay	Retrieval	
Büchel et al. (1999)	fMRI	3 male and 3 female participants, age: 25–36, no information on handedness No inclusion criteria	**OLM tasks:** Ten objects were presented sequentially in one of 10 locations for 2.5 s. Participants had to name the objects	Control task (not specified) No duration available	**OLM tasks (no analysis):** Cued recall: Participants were spatially cued with a nonsense shape. They had to vocally respond with the name of the previously encoded object in this location Three sessions with eight trials of the OLM task followed by a second control condition (not specified) were conducted	Functional connectivity analysis between six right-hemisphere regions (striate cortex, dorsal extrastriate cortex, posterior parietal cortex, lateral parietal cortex, posterior inferotemporal cortex = fusiform gyrus, anterior inferotemporal cortex = parahippocampal gyrus). Selected from individual participant analyses of evoked responses, the connections based on the anatomical model of the visual system Encoding OLM: Changes in connections between regions across the eight trials of the three sessions: - Increase of the excitatory influence of the right posterior parietal cortex on the right fusiform gyrus - Decrease of the excitatory influence of the right striate cortex on the dorsal extrastriate cortex
Cansino et al. (2002)	fMRI	22 right-handed participants, 2 participants excluded because of not enough incorrect responses, 3 participants excluded because of near-chance performance. Remaining: 15 female and 2 male participants, age: *M* = 24.6, 20–37, years of education: *M* = 14.6, 13–18 No inclusion criteria	**OLM tasks:** A cross dividing the screen into four quadrants was continuously displayed. 90 objects (half artificial, half natural) were presented sequentially for 1 s each randomly, but with the same probability, in one of the four quadrants (ISI: 2.6–10.4 s). Participants had to indicate by button presses with the right hand whether the objects were artificial or natural. Trials were intermixed with 45 visual fixation null events	No task 4 min	**OLM tasks:** Recognition/cued recall: The 90 encoded objects as well as 45 new objects (half artificial, half natural) were presented subsequently in random order in the center of the screen for 1 s each (ISI: 3–12 s). Old/new judgments had to be made by button presses with the right hand. If the object was judged as old, the quadrant in which it was presented during encoding had to be indicated by button presses with the right hand. Participants were instructed to guess in case they were unable to remember the correct location. Trials were intermixed with 45 visual fixation null events	Encoding correct > encoding false (> null events): Left superior frontal gyrus, left inferior frontal gyrus, bilateral precentral gyrus, paracentral lobule, left lateral parietal cortex, left superior temporal sulcus, right lateral occipital cortex, bilateral fusiform gyrus, left nucleus accumbens, left cerebellum (Null events >) retrieval correct > retrieval false: Left medial frontal gyrus, left superior frontal gyrus, right posterior insula, right middle temporal gyrus, right middle/inferior temporal gyrus, right lateral parietal cortex, medial occipital cortex, left middle occipital gyrus, right inferior occipital gyrus, right lingual gyrus, left parahippocampal gyrus, right hippocampal formation, right amygdala, left caudate nucleus, bilateral cerebellum
de Rover et al. (2008) Experiment 2	fMRI	10 female and 10 male right-handed participants, age: *M* = 25, 19–33, years of education: *M* = 19, *SD* = 3 Inclusion criteria: Right-handed according to Edinburgh handedness questionnaire, normal or corrected-to-normal vision	**OLM tasks (no analysis):** Two conditions: In each, 90 objects (45 living and 45 non-living) and their locations had to be encoded in sets of nine displayed in 3x3-grids for 3.3 s each. Participants had to make living/non-living decisions by button presses for each object. Conditions: 1) The to-be-encoded object was indicated by a red frame while all nine objects were visible. 2) Each object was presented individually in a red frame	A 3x3-grid with nine novel objects (five living, four non-living) changing their locations in each trial, was presented. Participants had to indicate if object in blue frame was at same location as in trial before. Duration: 29.7 s	**OLM tasks:** Cued recall: The encoded objects appeared sequentially for 3.3 s each below an empty 3x3-grid which was numbered from A1 to C3. Their correct locations had to be indicated by button presses with the left and right hands The OLM task was conducted in 20 cycles in two runs of 10 cycles each. A cycle consisted of the encoding of a set of nine objects, a distractor phase of 29.7 s, cued recall of the encoded set of nine objects, and a visual fixation phase of 29.7 s	Retrieval of OLM (conditions 1 + 2) > visual fixation: Bilateral prefrontal (Brodman areas 6/8/9/44/45/46), bilateral temporal (Brodman area 37), bilateral mediotemporal (Brodman area 36), bilateral parietal (Brodman areas 7, 23/31, 39/40), bilateral occipital regions (Brodman areas 17/18/19), bilateral thalamus, bilateral caudate/putamen, left putamen/globus pallidus Retrieval of OLM all objects present during encoding > retrieval of OLM only one object present during encoding: Bilateral occipital regions (Brodman areas 17/18/19) Retrieval of OLM only one object present during encoding > retrieval of OLM all objects present during encoding: Bilateral thalamus, bilateral globus pallidus

Hales & Brewer (2013)	fMRI	10 female and 7 male participants, age: *M* = 25.3, *SD* = 2.8, 2 participants excluded because of poor performance, 1 participant excluded because of scanning artifacts, no information on handedness Inclusion criteria: Normal or normal-to-corrected vision	**OLM tasks:** 64 2x2-grids were shown sequentially for 2 s each with a circle in one of the cells, followed by a fixation cross in the center of the screen for 0.5 s, a blank screen for 0–13 s, and a screen with an object in its center for 2 s. After a blank screen was presented for 0.5–13.5 s, the next trial began. Participants had to imagine the object in the cell indicated by the circle and encode its location **Control tasks**: *Object memory:* Same as in OLM tasks, only there was no circle in the grids and participants had to encode the object only Trials of both tasks were intermixed	No task Time for leaving the scanner	**OLM tasks (no imaging):** Recognition/cued recall: After object recognition (control task), participants had to indicate the encoded location of an encoded object by pressing four different buttons representing the four cells of the 2x2-grids or a fifth button indicating that the object was new or a sixth button if they were unsure about the objects' location. Self-paced **Control tasks (no imaging):** *Object memory:* 128 encoded and 40 new objects were shown subsequently in the center of the screen. Participants had to rate their confidence of the object being old or new on a six-point-rating scale from "definitely new" to "definitely old" with button presses. Self-paced	Encoding OLM > encoding object memory (only rated as "definitely old" during object retrieval) during presentation of grids: Right superior frontal gyrus, left middle occipital gyrus, bilateral superior parietal areas Encoding OLM correct location during OLM retrieval > encoding OLM incorrect location during OLM retrieval (only rated as "definitely old" during object retrieval) during presentation of grids: Right middle frontal gyrus, left cerebellum, bilateral cingulate areas
Johnsrude et al. (1999)	PET	6 male and 6 female right-handed participants, age: *M* = 22.5, 18–33 Inclusion criteria: No history of neurological or psychiatric illness	**OLM tasks (no imaging):** Eight objects were presented sequentially in unique locations with two white landmarks at constant positions. After having encoded the object and its location, participants touched the screen and the next object appeared 1 s later. The set of eight objects was shown four times in random order	No task Instructions Approx. 10 min	**OLM tasks:** Associative recognition: Eight pairs of identical objects were subsequently presented, one object being in its encoded location and the other object in the location of one of the seven other encoded objects. The object in the encoded location had to be touched and 1 s later the next pair was presented. The set of eight pairs was shown four times in random order. Different displays and retrieval cues were used: 1) Fixed display with landmarks: Display in same position as during encoding with the two landmarks shown at encoding. 2) Shifted display with landmarks: The display shifted position from the encoded one each trial, although all elements including the two landmarks maintained their spatial relationship to each other. 3) Fixed display with objects: Display in same position as during encoding shown with two other encoded objects in their encoded locations. 4) Shifted display with objects: The display shifted position from the encoded one each trial, although all objects maintained their spatial relationship to each other **Control tasks:** *Object-location perception:* Three hammers and one leaf were presented each in one of the four corners of the display. Participants had to touch the leaf. After 1 s, the next display was shown. 32 trials were conducted	Retrieval OLM tasks 1) – 4) > object-location perception: Right anterior parahippocampal gyrus, right posterior temporal cortex (inferior temporal gyrus), bilateral parietal (inferior parietal lobule), bilateral occipital (lingual gyrus), and bilateral cerebellar activations Retrieval OLM shifted > fixed displays: Right inferior parietal lobule/right posterior parietal cortex, right posterior temporal cortex, right middle frontal gyrus, right orbitofrontal cortex, right cerebellum, left inferior parietal lobule, left parahippocampal gyrus, left fusiform gyrus Retrieval OLM landmark cues > object cues: Right medial orbitofrontal area, right posterior inferior temporal gyrus, bilateral anterior middle frontal gyrus
Köhler et al. (1998a)	PET	12 male right-handed participants, age: *M* = 25.3, *SD* = 4.7	**OLM and control tasks (no imaging):** 22 displays of three unique objects in three unique locations were presented	No task 10 min	**OLM tasks**: Associative recognition: Pairs of an encoded display and a display in which one of the objects had changed	Functional connectivity analysis between six right-hemisphere regions (middle frontal gyrus, parieto-occipital sulcus, superior temporal sulcus, supramarginal gyrus, fusiform gyrus, cuneus) and the MTL. They were selected on the basis of a PLS with

		Inclusion criteria: No medical, neurological, or psychiatric disorder	sequentially for 3 s each and three times altogether		its location (ISI between displays: 0.75 s) were presented subsequently for 1 s (inter-pair interval: 2.25 s), twice in counterbalanced order. Participants had to indicate with button presses with the right hand which of the two displays was the altered one **Control tasks:** *Object memory:* Same as in OLM tasks but pairs of an encoded display and a display in which one of the objects had been replaced by a novel one were presented *Location perception:* Pairs of displays with three unique objects in three unique locations (ISI between displays: 0.75 s) were presented subsequently for 1 s (inter-pair interval: 2.25 s), twice in counterbalanced order. The displays were either the same or in one display the location of one of the objects had been changed. Participants had to indicate with button presses with the right hand whether the displays in a pair were identical or different *Object perception*: Same as location perception, but in altered displays one of the three objects had been replaced by a new one	OLM and three control tasks with three factors: Type of processing (retrieval vs. perception), type of information (object or location), and interaction of both. The right MTL was included in the neuroanatomic model based on theoretical grounds Retrieval OLM vs. retrieval object memory: - Excitatory vs. inhibitory influence of the right parieto-occipital sulcus/right supramarginal gyrus on the right MTL - Inhibitory vs. excitatory influence of the right fusiform gyrus/right superior temporal sulcus on the right MTL - Excitatory vs. inhibitory influence of the right fusiform gyrus/right superior temporal sulcus on the right middle frontal gyrus - Inhibitory vs. excitatory influence of the right parieto-occipital sulcus/right supramarginal gyrus on the right middle frontal gyrus
Köhler et al. (1998b)	PET	12 male right-handed participants, age: M = 25.3, SD = 4.7 Inclusion criteria: No medical, neurological, or psychiatric disorder (same as in Köhler et al., 1998a)	**OLM and control tasks (no imaging):** 22 displays of three unique objects in three unique locations were presented sequentially for 3 s each and three times altogether	No task 10 min	**OLM tasks**: Associative recognition: Pairs of an encoded display and a display in which one of the objects had changed its location (ISI between displays: 0.75 s) were presented subsequently for 1 s (inter-pair interval: 2.25 s), twice in counterbalanced order. Participants had to indicate with button presses with the right hand which of the two displays was the altered one **Control tasks:** *Object memory:* Same as in OLM tasks but pairs of an encoded display and a display in which one of the objects had been replaced by a novel one were presented *Location perception:* Pairs of displays with three unique objects in three unique locations (ISI between displays: 0.75 s) were presented subsequently for 1 s (inter-pair interval: 2.25 s), twice in counterbalanced order. The displays were either the same or in one display the location of one of the objects had been changed. Participants had to indicate with button presses with the right hand whether the displays in a pair were identical or different *Object perception*: Same as location perception, but in altered displays one of the three objects had been replaced by a new one	PLS with OLM and three control tasks with three factors: Type of processing (retrieval vs. perception), type of information (object or location) and interaction of both Retrieval OLM > retrieval object memory: Left lateral cerebellum

Moscovitch et al. (1995)	PET	12 male and 1 female right-handed young participants (no age specifications) Inclusion criteria: No medical, neurological, or psychiatric disorder	**OLM and control tasks (no imaging):** Participants had to encode 28 displays of three unique objects in unique spatial configurations in an invisible 6x8-grid. Displays were presented five times in random order	No task No available duration	**OLM tasks:** Associative recognition: Pairs of an encoded display and a display in which one of the objects had changed its location (ISI between displays: 0.75 s) were presented subsequently for 1 s (inter-pair interval: 2.25 s), twice in counterbalanced order. Participants had to indicate with button presses of the right hand which of the two displays was the encoded one **Control tasks:** *Object memory:* Same as in OLM tasks, but pairs of an encoded display and a display in which one of the objects had been replaced by a novel one were presented *Object-location perception:* Two of the encoded 28 displays (either two identical or two different ones) were shown and identical/different decisions had to be made with button presses of the right hand	Retrieval OLM > retrieval object memory: Right inferior parietal lobule (supramarginal gyrus) Retrieval OLM > object-location perception: Bilateral cuneus, right inferior temporal/fusiform gyrus, right supramarginal gyrus/inferior parietal lobule, right inferior midfrontal gyrus, bilateral anterior superior cerebellum
Owen et al. (1996a)	PET	6 male and 6 female right-handed participants, age: *M* = 26.8, 18–35 Inclusion criteria: No history of neurological or psychiatric illness	**OLM tasks:** Encoding of eight objects which were presented in eight white squares sequentially. After finishing the encoding of one object, participants touched the screen and the next object appeared 1 s later. The set of eight objects was presented four times in random order **Control tasks:** *Object memory:* Same as in OLM tasks, only objects were presented in the center of the screen	No task Instructions and practice trials Approx. 10 min	**OLM tasks:** Associative recognition: Eight pairs of identical objects were presented sequentially. One object of the pair was in the encoded location, the other object's location had been occupied by another of the eight encoded objects during encoding. The encoded object-location association had to be indicated by touch. After 1 s, the next pair appeared. The eight pairs were presented four times in random order. **Control tasks:** *Object memory:* Same as in OLM tasks, only pairs of objects were presented sequentially in the center of the screen. One object of the pair was an encoded one, the other an object of the same type but with different perceptual features	Encoding OLM > encoding object memory: Bilateral posterior parietal cortex, bilateral ventral prestriate cortex, right dorsal prestriate cortex, left premotor cortex, right cerebellum, midline striate cortex Retrieval OLM > retrieval object memory: Bilateral posterior parietal cortex, bilateral precuneus, left posterior cingulate cortex, left medial posterior parietal cortex, left prestriate cortex, right premotor cortex, midline striate cortex
Owen et al. (1996b)	PET	6 male and 6 female right-handed participants, age: *M* = 26.8, 18–35 Inclusion criteria: No history of neurological or psychiatric illness (same as in Owen et al., 1996a)	**OLM tasks:** Encoding of eight objects which were presented in eight white squares sequentially. After finishing the encoding of one object, participants touched the screen and the next object appeared 1 s later. The set of eight objects was presented four times in random order (same as in Owen et al., 1996a) **Control tasks:** *Location memory:* Same as in OLM tasks, only white squares (locations) were presented alone	No task Instructions and practice trials Approx. 10 min	**OLM tasks:** Associative recognition: Eight pairs of identical objects were presented sequentially. One object of the pair was in the encoded location, the other object's location had been occupied by another of the eight encoded objects during encoding. The encoded object-location association had to be indicated by touch. After 1 s, the next pair appeared. The eight pairs were presented four times in random order. (same as in Owen et al., 1996a) **Control tasks:** *Location memory:* Same as in OLM tasks, only eight pairs of white squares were presented sequentially.	Encoding OLM > encoding location memory: Bilateral anterior fusiform gyrus, bilateral prestriate cortex Retrieval OLM > retrieval location memory: Right anterior parahippocampal gyrus/entorhinal cortex, bilateral prestriate cortex, bilateral striate cortex

					One square of the pair was in the encoded location, the other square in a location that had not been occupied in any previous trial	
Sommer et al. (2005a)	fMRI	21 participants recruited, 6 participants excluded because of poor performance. Remaining: 7 female and 8 male right-handed participants, age: *M* = 24.4, 20–28 No inclusion criteria	**OLM tasks:** In the center of the screen, eight artificial and eight natural objects were presented with their name below for 2.5 s. Participants had to press a button when they recognized an object and read its name. Afterwards, the 16 objects were presented subsequently for 2 s in one of 16 black boxes shown on the screen (ISI: 2.5–3.5 s). The location of the next object was cued for 0.5 s by a change of the color of its box. Participants had to make an artificial/natural decision on each object with button presses	Counting aloud backwards from a number between 80–100 in steps of three No available duration	**OLM tasks (no imaging):** Cued recall: Two different retrieval cue types: 1) objects or 2) locations. All encoded object-location associations were probed with each of the two retrieval cues. 1) Object was presented in center of screen for 3 s, followed by the encoded empty array of 16 boxes. Participants could select as many different boxes as necessary to include the encoded location or indicate with the mouse that they forgot the location. 2) The empty encoded array of 16 boxes was displayed with one box marked with a question mark for 3 s, followed by downsized pictures of the encoded 16 objects. Participants could select as many objects as necessary to include the encoded object or indicate with the mouse that they forgot the object Ten sessions of the OLM task were conducted	Brain regions with significant positive correlation of brain activity during encoding with memory performance at retrieval with both retrieval cues: Bilateral parahippocampal cortex, left fusiform gyrus, left anterior inferior prefrontal cortex Brain regions with significant positive correlation of brain activity during encoding with memory performance at retrieval with objects as retrieval cues: Right anterior MTL, left parahippocampal cortex, left rostral precentral sulcus, left angular gyrus, left lingual gyrus Brain regions with significant positive correlation of brain activity during encoding with memory performance at retrieval with locations as retrieval cues: No specific brain regions
Sommer et al. (2005b)	fMRI	8 female and 7 male right-handed participants, age: *M* = 28.8, 22–35 No inclusion criteria	**OLM tasks:** In the center of the screen, eight artificial and eight natural objects were presented with their name below it for 2.5 s. Participants had to press a button when they recognized an object and read its name. Afterwards, the 16 objects were presented subsequently for 2 s in one of 16 black boxes shown on the screen (ISI: 2.5–3.5 s). The location of the next object was cued for 0.5 s by a change of the color of its box. Participants had to make an artificial/natural decision on each object with button presses	Counting aloud backwards from a number between 80–100 in steps of three No available duration	**OLM tasks (no imaging):** Cued recall: Each of the encoded objects was presented in the center of the screen for 2.5 s, followed by the encoded array of 16 black boxes. Participants could select as many different boxes as necessary to include the encoded location or indicate with the mouse that they forgot the location Ten sessions of the OLM task were conducted	Brain regions with significant positive correlation of brain activity during encoding with memory performance at retrieval: Right calcarine, right dorsal extrastriate cortex, bilaterial superior parietal cortex, left angular gyrus, bilateral fusiform gyrus, bilateral parahippocampal gyrus, bilateral frontal eye fields, left rostral precentral sulcus, left anterior inferior prefrontal cortex, left posterior inferior prefrontal cortex, right dorsolateral prefrontal cortex, left anterior cingulate gyrus

Note: OLM = Object-location memory. MTL = Medial temporal lobe.

Among the studies exploring OLM encoding, Owen and colleagues (1996a, b) subtracted brain activity during object and location encoding, respectively, from brain activity during OLM encoding. Sommer and colleagues (2005a, b) identified brain regions whose activity during OLM encoding correlated positively with later cued OLM recall performance. Cansino and colleagues (2002) and Hales and Brewer (2013) subtracted brain activity during the encoding of later incorrectly recalled object-location associations from brain activity during the encoding of later correctly recalled object-location associations. Finally, Büchel and colleagues (1999) used a functional connectivity analysis to investigate the change of functional connections between six brain regions of the right hemisphere during the course of several OLM encoding trials.

With regard to the studies analyzing brain regions involved in OLM retrieval, Cansino and colleagues (2002) subtracted brain activity during incorrect OLM recall trials from brain activity during correct OLM recall trials. Moreover, Köhler and colleagues (1998) performed a functional connectivity analysis contrasting the functional connections between six brain regions of the right hemisphere during OLM recognition with those during object recognition. In all studies, brain activity during one or two control tasks was subtracted from brain activity during OLM retrieval. Following types of control tasks were employed: visual fixation (de Rover et al., 2008), object-location perception (Johnsrude et al., 1999; Moscovitch et al., 1995), object memory (Köhler et al., 1998a, b; Moscovitch et al., 1995; Owen et al., 1996a), and location memory (Owen et al., 1996b).

In all reviewed neuroimaging studies, computerized OLM paradigms were used, presenting 3–90 pictures of everyday nameable objects in grids or on the empty computer screen. Only in one study (Johnsrude et al., 1999), two landmarks were also presented during all OLM encoding trials as well as in half of the retrieval trials. Furthermore, the spatial relations between the objects' locations were always categorical. Johnsrude and colleagues

(1999) used four different retrieval conditions. In two of them, the display in which the object-location associations were presented shifted its location from encoding to retrieval, thereby clearly posing higher demands on allocentric location processing. In the two other of their four retrieval conditions, the authors changed features of the background environment from encoding to retrieval, thus prohibiting the use of background characteristics as retrieval cues. In all other studies, the display was in the same position during OLM encoding and retrieval. Consequently, these OLM tasks could be solved with egocentric location processing. However, they probably also induced allocentric location processing, since participants most certainly used the borders of the computer screen or the characteristics of the grids as body-independent spatial cues.

In four studies (de Rover et al., 2008; Köhler et al., 1998a, b; Moscovitch et al., 1995), several to-be-encoded object-location associations were presented simultaneously during encoding, whereas in the remaining eight studies each of the to-be-encoded object-location associations appeared alone. De Rover and colleagues (2008) employed both encoding conditions. Solely in the study by Hales and Brewer (2013), first an object and then its location was presented, and participants were asked to imagine the object in this location. In all other studies, the objects and their locations were displayed concurrently. In addition, participants had to name the objects in one study (Büchel et al., 1999) or make artificial/natural decisions in four other studies (Cansino et al., 2002; de Rover et al., 2008; Sommer et al., 2005a, b). In both studies by Sommer and colleagues (2005a, b), the to-be-encoded objects were first presented on their own with their names below and participants were asked to read them. Only afterwards, OLM encoding was initiated.

In two studies (Cansino et al., 2002; de Rover et al., 2008), OLM retrieval was tested with cued recall. In all other studies, OLM retrieval was assessed with associative recognition. In addition, all studies which considered retrieval performance in their OLM encoding

analyses (Cansino et al., 2002; Hales & Brewer, 2013; Sommer et al., 2005a, b) implemented cued OLM recall using objects as retrieval cues. Only Sommer and colleagues (2005a) also cued OLM retrieval with locations. In Cansino and colleagues (2002) and Hales and Brewer (2013), object recognition was tested first (the encoded and other objects were presented) and if an object was identified as encoded, recall for its location was then assessed. In the other studies using cued recall, only the encoded objects or locations were presented.

In five of the seven studies which analyzed OLM encoding, motor responses were required during this memory phase. Whereas they consisted of button presses in the studies by Cansino and colleagues (2002) and Sommer and colleagues (2005a, b), Owen and colleagues (1996a, b) used screen touches. In the eight studies which investigated OLM retrieval, motor responses comprised button presses in five of these studies (Cansino et al., 2002; de Rover et al., 2008; Köhler et al., 1998a, b; Moscovitch et al., 1995) and screen touches in the remaining three studies (Johnsrude et al., 1999; Owen et al., 1996a, b). In all studies with the exception of the study by de Rover and colleagues (2008), motor responses were controlled for by applying the same nature of response in the control tasks.

Only one study (de Rover et al., 2008) provided detailed information about both the content and duration of the delay between OLM encoding and retrieval phases. In contrast, Moscovitch and colleagues (1995) did not report any specific details about the delay. All other studies described either the content or provided the length of the delay. In these studies (certainly also in Moscovitch et al., 1995), some time passed between the end of the encoding and the beginning of the retrieval task, thus all studies investigated delayed OLM retrieval.

Study samples included 6–22 participants. Due to poor performance or not enough incorrect responses as well as imaging artifacts, Hales and Brewer (2013) had to exclude three participants, Cansino and colleagues (2002) five participants, and Sommer and colleagues (2005a) six participants. Therefore, 6–17 participants were included in the final imaging

analyses. Participants were aged 18–36 years, however, one study (Moscovitch et al., 1995) did not provide information about the age of its participants. Two studies (Köhler et al., 1998a, b) included only male participants, while in one study (Moscovitch et al., 1995) all participants were men besides one woman, and in another study (Cansino et al., 2002) all participants were women with the exception of one man. In the remaining studies, male and female participants were represented in equal or almost equal numbers. Merely six studies (Johnsrude et al., 1999; Köhler et al., 1998a, b; Moscovitch et al., 1995; Owen et al., 1996a, b) verified the absence of previous and/or current neurological as well as psychiatric and/or medical disorders in their participants, thus providing some evidence that they were indeed healthy. In addition, two studies (de Rover et al., 2008; Hales & Brewer, 2013) required their participants to have normal or corrected-to-normal vision. All studies besides Büchel and colleagues (1999) and Hales and Brewer (2013), who did not provide information on the handedness of their participants, included right-handed participants. However, only in the study by de Rover and colleagues (2008), right-handedness was verified with a test.

Of the eight studies investigating the involvement of brain regions in OLM retrieval, de Rover and colleagues (2008) subtracted brain activity during the visual fixation baseline from brain activity during cued OLM recall. The results revealed increased activity in bilateral frontal, (medio)temporal, parietal, and occipital regions as well as in the bilateral thalamus, the bilateral caudate/putamen, and the left putamen/globus pallidus. Hence, similar brain regions as indicated by the lesion studies on delayed cued categorical OLM recall (Kessels et al., 2000, 2002; Stepankova et al., 2004) were activated with the exception of frontal regions, the thalamus, and the basal ganglia. The activity in the latter two brain regions might have been caused by the button presses required in the OLM task trials, but not during the visual fixation trials. Similar to the lesion study by Smith and colleagues (1995), frontal regions may have been involved because of the high interference inherent in de Rover and colleagues'

(2008) OLM paradigm. It required the encoding of 10 different sets of nine objects presented in two different ways at the same nine locations. The retrieval of object-location associations, which were encoded while the other eight object-location associations were also visible, elicited increased brain activity in bilateral occipital regions compared to the retrieval of object-location associations which were presented one at the time during encoding. In contrast, the retrieval of object-location associations which were displayed consecutively during encoding evoked greater brain activity in the bilateral thalamus and the bilateral globus pallidus. The authors explained the differences in brain activity between the two retrieval conditions by the use of distinct strategies. They proposed that in order to guide the retrieval of the location of a currently presented single object in the first condition, participants tried to recall the spatial arrangement of all nine object-location associations because they had been present in all encoding trials of this condition. Contrarily, they remembered the temporal order of the nine object-location associations across the encoding trials in the second condition. Therefore, the thalamus and the globus pallidus may be involved in OLM tasks in which several object-location associations are presented subsequently during encoding. Moreover, their temporal order can be used to facilitate retrieval.

Similarly, Johnsrude and colleagues (1999) displayed several object-location associations one after the other during encoding. However, two landmarks were additionally present at the same locations during all encoding trials. OLM retrieval was tested with associative recognition rather than cued recall. One of the encoded objects was presented at its location during encoding as well as at the location of one of the other objects during encoding, and participants were asked to touch the encoded object-location association on the screen. Moreover, as mentioned before, four different retrieval conditions were investigated. In two of the retrieval conditions, the two landmarks that were present during all encoding trials were also shown in their original locations during retrieval. In contrast, the other two

conditions contained objects other than the two encoded ones and were displayed at their locations instead. In the first two retrieval conditions, cues present during all encoding trials (landmarks or display borders) could be used to facilitate OLM retrieval, whereas in the other two retrieval conditions only the spatial relations between the objects' locations could guide recognition, thereby enforcing higher OLM demands. In addition, in two of the retrieval conditions, the whole display of object- and/or landmark-location associations remained in the same position during encoding and retrieval, while it shifted its position in the two other retrieval conditions, consequently posing increased cognitive requirements on allocentric location processing.

Johnsrude and colleagues (1999) found increased activity in the right anterior parahippocampal gyrus, the right inferior temporal gyrus, the bilateral inferior parietal lobule, the bilateral lingual gyrus, and the bilateral cerebellum during all OLM retrieval conditions compared to an object-location perception control task, indicating an involvement of these brain regions in object memory, location memory, and/or object-location binding. There was a great overlap between these brain regions and those reported by de Rover and colleagues (2008) with the exception of the differential involvement of subcortical regions. This might have been caused by a) the use of a control task in which the same motor reactions as in the OLM task were required, b) a different type of motor response (touch) in the OLM task, or c) a different type of retrieval (i.e., recognition whereby temporal order information could not be used since object-location associations were presented four times in random order during encoding). Lesion studies using a similar OLM design (Holdstock et al., 2002; King et al., 2002, 2004) had instead indicated the bilateral involvement of the hippocampus in both object memory and OLM. However, Johnsrude and colleagues (1999) mentioned that the spatial resolution of their PET technique was so low that activity in the right parahippocampal gyrus could not be clearly differentiated from activity in the right hippocampus. While the lesion

study by Kessels and colleagues (2000) pointed to an involvement of the right posterior parietal cortex in object-location perception, object memory, location memory, and OLM, Johnsrude and colleagues (1999) clearly demonstrated that the right (and the left) posterior parietal cortex, particularly the inferior lobule, is involved in memory and not only perception subprocesses of OLM. Moreover, the contrasts between the different sets of retrieval conditions (landmarks present > only object-location associations present; shifted displays > fixed displays) indicated that the right inferior temporal gyrus is necessary for using external cues of the environment to guide OLM retrieval and that the bilateral inferior parietal lobule and the right cerebellum (in addition to the left parahippocampal gyrus and the left fusiform gyrus) are important for allocentric OLM retrieval. Contrarily, lesion studies manipulating the demands on allocentric location processing of objects (King et al., 2002, 2004) had only suggested the key role of the bilateral hippocampus for this type of OLM.

Moscovitch and colleagues (1995) contrasted brain activity during delayed associative categorical OLM recognition with brain activity during an object-location perception task. Similar to the study by Johnsrude and colleagues (1999), they found increased activity in the right inferior temporal gyrus/fusiform gyrus, the right inferior parietal lobule/supramarginal gyrus, and the bilateral cerebellum during the OLM task, thus supporting the importance of these regions but not that of the right parahippocampal gyrus for OLM. Additionally, the bilateral cuneus and the right inferior midfrontal gyrus were activated to a greater degree. This might have been caused by the presentation of three object-location associations simultaneously during encoding and retrieval and/or by the use of a different motor response (button presses). However, the latter fact also indicates that the bilateral cerebellum may be implicated directly in memory processes involved in OLM. Moscovitch and colleagues (1995) further applied an object memory control task. Interestingly, only the right inferior parietal

lobule/supramarginal gyrus was more activated during the OLM task, pointing to its special role for location memory and/or object-location binding.

With a slight modification, the same OLM and object memory tasks were employed in a PET study by Köhler and colleagues (1998b). However, they only found the left lateral cerebellum to be more activated during the OLM compared to the object memory task, suggesting that this structure may also be specifically involved in location memory and/or object-location binding processes. Owen and colleagues (1996a) subtracted brain activity during delayed object recognition from brain activity during delayed associative categorical OLM recognition. They reported increased activity in the bilateral posterior parietal cortex, the bilateral precuneus, the left posterior cingulate cortex, the right premotor cortex, the left prestriate cortex, and the midline striate cortex during the OLM tasks. Consequently, their findings also emphasize the importance of the posterior parietal cortex for location memory and/or object-location binding processes in OLM. These results are in line with the two lesion studies on categorical location memory and OLM, the first (Kessels et al., 2004) demonstrating neither bilateral involvement of the amygdala nor of the hippocampus in both abilities and the second (van Asselen et al., 2008) no specialization of one hemisphere for categorical OLM.

In a second PET study, Owen and colleagues (1996b) applied the same OLM task, but compared it to a location memory task. During the OLM task, the right anterior parahippocampal gyrus/entorhinal cortex as well as the bilateral prestriate and striate cortices showed increased activity. This implies that the right parahippocampal gyrus may be particularly specialized for object memory and/or object-location binding processes. This result coincides with the findings from seven lesion studies (Bohbot et al., 1998, 2000; Crane & Milner, 2005; Kessels et al., 2004; Pigott & Milner, 1993; Stepankova et al., 2004; van Asselen et al., 2008), but contradicts the findings by Kessels and colleagues (2000, 2002)

pointing to the involvement of only posterior and occipital regions in categorical OLM and object memory, the findings by van Asselen and colleagues (2009) suggesting a left-lateralization of categorical OLM, and by Holdstock and colleagues (2002) indicating the bilateral involvement of the hippocampus in both categorical OLM and object memory.

In an event-related fMRI study, Cansino and colleagues (2002) contrasted brain activity during correct trials with that during incorrect trials of a delayed cued categorical recall OLM task. They found the left medial frontal gyrus, the left superior frontal gyrus, the right posterior insula, the right middle/inferior temporal gyrus, the right lateral parietal cortex, the left parahippocampal gyrus, the right hippocampus, the right amygdala, the medial occipital cortex, the left middle occipital cortex, the right lingual gyrus, the left caudate nucleus, and the bilateral cerebellum to be activated to a greater extent during correct OLM retrieval trials. The OLM task applied in this study was more similar to that used by de Rover and colleagues (2008) than to the ones assessed in the other above described studies. There was also a greater overlap between brain regions reported to be explicitly involved in OLM retrieval by Cansino and colleagues (2002) and by de Rover and colleagues (2008) than between brain regions reported by Cansino and colleagues (2002) and the other studies. However, the findings also confirmed the previously demonstrated involvement of the left parahippocampal gyrus, the right inferior temporal gyrus, and the bilateral cerebellum in delayed OLM retrieval. Notably, it was the only functional neuroimaging study that showed a specific contribution of the right hippocampus and the right amygdala to OLM retrieval and as such supported the findings from the lesion studies indicating the importance of these regions for OLM.

Finally, in the second study by Köhler and colleagues (1998a) in which the same paradigm was used as in the first study, functional connectivity between six right hemisphere regions (middle frontal gyrus, parieto-occipital sulcus, superior temporal sulcus, fusiform gyrus, supramarginal gyrus, and cuneus) and the MTL during the OLM and the object

memory task was analyzed. The results revealed excitatory influences of the right parieto-occipital sulcus and the right supramarginal gyrus on the right MTL and of the right fusiform gyrus and the right superior temporal sulcus on the right middle frontal gyrus during the OLM task, whereas during the object memory task all the described functional connections were inhibitory. Hence, these regions appear to work together to support delayed location and/or object-location association retrieval. However, not all of these brain regions have been shown to be specialized for OLM retrieval in the other reviewed neuroimaging studies.

Owen and colleagues (1996a, b) as well as Cansino and colleagues (2002) recorded brain activity during the encoding phases of their tasks. Owen and colleagues (1996a) found a great overlap between brain regions more activated in OLM than in object encoding and those more activated in OLM than in object recognition, that is, the bilateral posterior parietal cortex, the left prestriate cortex, and the midline striate cortex. Both contrasts also highlighted the premotor cortex – in the left hemisphere during encoding and in the right hemisphere during retrieval – which is in accordance with the HERA framework (Nyberg et al., 1996; Tulving et al., 1994). During encoding, increased activity in the right cerebellum was found during the OLM task, whereas during retrieval the bilateral precuneus and the left posterior cingulate cortex were additionally activated during OLM versus object recognition. In the second study by Owen and colleagues (1996b), activity in the bilateral anterior fusiform gyrus and the bilateral prestriate cortex was observed during OLM compared to location encoding, the latter brain region being also more activated during OLM than location recognition. However, there was additional activity in the right anterior parahippocampal gyrus/entorhinal cortex. Consequently, this brain region may be especially specialized for the retrieval of objects and/or object-location associations, whereas the bilateral fusiform gyrus may serve the encoding of this information. Finally, along the lines of the second study by Owen and colleagues (1996b), Cansino and colleagues (2002) detected little overlap (only the left

superior frontal gyrus, the left cerebellum, and the lateral parietal cortex (left during encoding, right during retrieval)) between brain activity during the encoding of later correctly versus incorrectly retrieved object-location associations and brain activity during correct versus false OLM retrieval trials. Similarly, they found only a selective involvement of mediotemporal regions (left parahippocampal gyrus, right hippocampus, right amygdala) in OLM during retrieval, indicating their involvement in OLM consolidation.

Four more studies investigated brain regions involved in OLM encoding. In both studies by Sommer and colleagues (2005a, b), the same fMRI OLM paradigm was employed during OLM encoding, and OLM retrieval was tested outside the scanner with a cued recall task. In both studies, positive correlations were found between brain activity in the left parahippocampal gyrus, the left rostral precentral sulcus, and the left angular gyrus during OLM encoding and cued recall performance, thus stressing the involvement of the parahippocampal gyrus in OLM encoding. In one of the studies (Sommer et al., 2005b), brain activity during OLM encoding was also positively correlated with cued recall performance in frontal, parietal, and occipital regions as well as in the bilateral parahippocampal gyrus and the bilateral fusiform gyrus. In the other study (Sommer et al., 2005a), an additional cued recall condition was included in which locations instead of the usually used objects served as retrieval cues. No significant correlations were found between brain activity during encoding and cued retrieval performance. When both conditions were collapsed, brain activity in the bilateral parahippocampal cortex, the left fusiform gyrus, and the left anterior inferior prefrontal cortex correlated positively with later recall performance. Again, this points to the importance of the bilateral involvement of the parahippocampal gyrus and the fusiform gyrus in OLM encoding.

In contrast, Hales and Brewer (2013) employed an event-related fMRI paradigm. During encoding, they first presented the objects and then their locations and asked

participants in these second trials to imagine the objects at their respective locations. Similarly, object recognition was assessed first followed by cued object-location association recall. During object recognition, participants had to rate their confidence that a presented object was old or new on a six-point rating scale ranging from “definitely new” to “definitely old”. Hales and Brewer (2013) subtracted brain activity elicited during the object encoding trials from brain activity elicited during the OLM encoding trials. However, only trials with objects rated as definitely old during object recognition were used. The right superior frontal gyrus and the bilateral superior parietal cortex were identified as brain regions with increased activity during OLM encoding. In line with Owen and colleagues (1996a), these findings support the specific role of bilateral parietal areas for location encoding and object-location binding. In addition, Hales and Brewer (2013) contrasted brain activity during the encoding of object-location associations that were later correctly recalled with brain activity during the encoding of object-location associations that were later incorrectly recalled. In this contrast, increased brain activity was observed in the right middle frontal gyrus as well as in bilateral cingulate areas, i.e., in other brain regions than those found to be activated when brain activity of later incorrectly recalled object-location associations was subtracted from brain activity of later correctly recalled object-location associations in the study by Cansino and colleagues (2002). However, in this contrast, other frontal brain regions (left superior frontal gyrus, left inferior frontal gyrus) were also activated to a greater degree.

In addition, Büchel and colleagues (1999) investigated functional connectivity changes between six brain regions of the right hemisphere (striate cortex, dorsal extrastriate cortex, posterior parietal cortex, lateral parietal cortex, fusiform gyrus, parahippocampal gyrus) across eight learning trials of three sessions. They observed an increase of the excitatory influence of the right posterior parietal cortex on the right fusiform gyrus and a decrease of the excitatory influence of the right striate cortex on the dorsal extrastriate cortex. They

interpreted these findings as correlates of an increased binding between object and location information during encoding, since the posterior parietal cortex seems to be involved in location encoding and the fusiform gyrus in object encoding.

Overall, the findings from the neuroimaging studies point to the importance of the posterior parietal cortex, the parahippocampal gyrus, the inferior temporal gyrus/fusiform gyrus, and the cerebellum in OLM. There was a tendency for a lateralization of these regions to the left during encoding and to the right during retrieval, but often both hemispheres were engaged. In addition, also frontal and occipital regions appear to be relevant. Generally, there was little overlap between frontal regions across the different studies, but if so, most often in the left superior frontal gyrus or the right middle frontal gyrus. There was also some indication of a stronger contribution of prefrontal regions in OLM cued recall than in OLM recognition. The involvement of occipital regions can be explained by the additional visual perceptual effort required for processing object-location associations in comparison to processing objects or locations alone. Among these regions, the posterior parietal cortex seems to be particularly specialized for location memory and the inferior temporal gyrus/fusiform gyrus and the parahippocampal gyrus for object memory. Interestingly, the posterior parietal cortex was implicated in both OLM encoding and retrieval, while the fusiform gyrus was mainly involved in OLM encoding, and the parahippocampal gyrus in OLM retrieval. In common with the lesion studies, the one neuroimaging study demonstrating an involvement of the right hippocampus and the right amygdala in OLM (Cansino et al., 2002) found these regions to be specifically activated during OLM retrieval, but not during encoding. Therefore, the mediotemporal regions found to be engaged in OLM may be particularly important for long-term retention of object-location associations. There was also some indication that the excitatory influence of the right posterior parietal cortex on the right fusiform gyrus increases during encoding. This might be the correlate of the object-location

binding process. In addition, the bilateral posterior parietal cortex, the left parahippocampal gyrus, the left fusiform gyrus, and the right cerebellum have been found to be important for delayed cued categorical OLM recall with high demands on allocentric location processing.

Changes in brain regions involved in intentional non-navigational episodic OLM across adulthood

Evidence from neuroimaging studies with healthy young and older adults

In Table 3, characteristics of participants, the features of the encoding, delay, and retrieval phases of the experimental OLM and possible control tasks as well as the results in terms of age differences in brain regions specialized for OLM of the reviewed neuroimaging studies with healthy young and healthy older adults studies are described in detail.

Two (Kukolja et al., 2009; Meulenbroek et al., 2010) of the three studies investigating age differences in brain regions involved in OLM were fMRI studies, the other a PET study (Schiavetto et al., 2002). Two of the studies specifically focused on OLM retrieval (Meulenbroek et al., 2010; Schiavetto et al., 2002), while Kukolja and colleagues (2009) examined both OLM encoding and retrieval. Meulenbroek and colleagues (2010) subtracted brain activity during a visual fixation baseline and Schiavetto and colleagues (2002) brain activity during object retrieval from brain activity during OLM retrieval. In contrast, Kukolja and colleagues (2009) subtracted brain activity during the encoding and retrieval of incorrectly recalled object-location associations from brain activity during the encoding and retrieval of correctly recalled object-location associations.

Table 3. Reviewed neuroimaging studies of age differences between young and older adults: Reference, neuroimaging method, participants, OLM and control task characteristics, and results

Reference	Neuro-imaging method	Participants	Task characteristics			Results
			Encoding	Delay	Retrieval	
Kukolja et al. (2009)	fMRI	11 female and 14 male young and 12 female and 13 male older right-handed participants included, 8 older and 3 young participants excluded because of poor performance, 4 young participants excluded because of not enough falsely retrieved locations. Remaining: 8 female and 10 male young (age: *M* = 24.0, 19–29, years of education: *M* = 16.4, *SD* = 1.9) and 7 female and 10 male older participants (age: *M* = 60.3, 52–77, years of education: *M* = 14.8 years, *SD* = 3.4) Inclusion criteria: Right-handedness according to Edinburgh handedness questionnaire, no history of neurological or psychiatric disorder, normal or corrected-to-normal vision No group differences for education, depression (BDI scores), verbal short-term memory (HAWIE-R Digit span), episodic verbal memory free delayed recall and delayed recognition (CERAD). Old > young: Crystallized intelligence (MWT-B), memory complaints (MAC-Q). Young > old: MMSE, word fluency (CERAD, FAS) VBM: Young > old: Gray matter volumes in bilateral insular, inferior prefrontal, superior parietal and cerebellar cortices, bilateral fusiform gyrus, right temporal pole. Old > young: Right amygdala	**OLM tasks:** A cross dividing the screen into four quadrants was continuously displayed. 64 objects (half artificial, half natural) were presented sequentially for 1 s each, randomly, but with the same probability, in one of the four quadrants (ISI: 1.6 s). Participants had to indicate by button presses with the right hand whether the objects were artificial or natural. Trials were intermixed with 32 null events in which only the cross was shown	No task 4 min	**OLM tasks:** Recognition/cued recall: The 64 encoded objects as well as 32 new (half artificial, half natural) objects were presented subsequently in random order in the center of the screen for 1.5 s each (ISI: 2.3 s). Old/new judgments had to be made by button presses with the left hand. If the object was judged as old, the quadrant in which it was presented during encoding had to be indicated by button presses with the right hand. Participants were instructed to guess in case they were unable to remember the correct location. Trials were intermixed with 32 null events in which only the cross was shown	**Behavioral:** Object recognition: Young = old Location recall: Young > old **fMRI:** ANOVA on correctly retrieved old objects with retrieval success (correct vs. false) and age (young vs. old) as main factors (same results when masked with age differences in gray matter volume) Encoding OLM, main effect of age: Young > old: Left fusiform gyrus, left inferior occipital gyrus Old > young: - Encoding OLM, age x retrieval success interaction: Greater activity for correct than false location retrieval: Young > old: Left fusiform gyrus Old > young: Right anterior cingulate gyrus Retrieval OLM, main effect of age: Young > old: Left lateral superior parietal cortex Old > young: Bilateral medial frontal gyrus, left supplementary motor area, bilateral inferior parietal cortex, left middle temporal gyrus, left anterior cingulate gyrus, left precuneus Retrieval OLM, age x retrieval success interaction: Greater activity for correct than false location retrieval: Young > old: Left hippocampus Old > young: -
Meulenbroek et al. (2010) Experiment 2	fMRI	10 female and 10 male young (age: *M* = 25, 19–33, years of education: *M* = 18, *SD* = 2) and 10 female and 10 male older right-handed participants (age: *M* = 65, 60–74, years of education: *M* = 17, *SD* = 0.6) Inclusion criteria: Right-handedness according to Edinburgh handedness questionnaire.	**OLM tasks (no analysis):** Two conditions: In each, 90 objects (45 living and 45 non-living) and their locations had to be encoded in sets of nine displayed in 3x3-grids for 3.3 s each. Participants had to make living/non-living decisions by button presses for each object. Conditions: 1) The to-be-encoded object was indicated	A 3x3-grid with nine novel objects (five living, four non-living) changing their locations in each trial,	**OLM tasks:** Cued recall: The encoded objects appeared sequentially for 3.3 s each below an empty 3x3-grid which was numbered from A1 to C3. Their correct locations had to be indicated by button presses with the left and right hands The OLM task was conducted in 20 cycles in two runs of 10 cycles each. A cycle consisted of	**Behavioral:** Young > old for both encoding conditions → Performance was used as covariate in all fMRI analyses **fMRI:** ANOVA with task (OLM conditions 1 vs. rest and 2 vs. rest) and age (young, old) as factors only on brain activity during OLM retrieval

		Older participants: No history of neurological or psychiatric disorder, no use of psychopharmacological drugs, no subjective memory problems, normal or corrected-to-normal vision	by a red frame while all nine objects were visible. 2) Each object was presented individually in a red frame	was presented. Participants had to indicate if object in blue frame was at same location as in trial before. Duration: 29.7 s	encoding of a set of nine objects, a distractor phase of 29.7 s, cued recall of the encoded set of nine objects, and a rest phase of 29.7 s	Retrieval OLM > rest, main effect of age: Young > old: - Old > young: Left superior temporal gyrus, right putamen, right insula, right caudate nucleus Retrieval OLM, age x type of retrieval interaction: Greater activity for condition 1 (all objects visible) than condition 2 (only one object visible): Young > old: - Old > young: Left middle temporal gyrus, left fusiform gyrus, left inferior temporal gyrus, right thalamus (pulvinar nucleus), right parahippocampal gyrus, right brainstem, left internal capsule, bilateral globus pallidus, left thalamus (lateral posterior nucleus), right thalamus (mediodorsal nucleus), right thalamus (ventral lateral nucleus)
Schiavetto et al. (2002)	PET	12 male right-handed young participants (age: *M* = 25.3, *SD* = 4.7) (same as in Köhler et al., 1998a, b), 11 male and 1 female right-handed older participants (*M* = 70.17, *SD* = 3.86) Inclusion criteria: No history of medical, neurological, or psychiatric disorder	**OLM and control tasks (no imaging):** 22 displays of three unique objects in three unique locations were presented sequentially for 3 s each, three times altogether for young and five times altogether for older participants	No task 10 min	**OLM tasks**: Associative recognition: Pairs of an encoded display and a display in which one of the objects had changed its location (ISI between displays: 0.75 s) were presented subsequently for 1 s (inter-pair interval: 2.25 s), twice in counterbalanced order. Participants had to indicate with button presses with the right hand which of the two displays was the altered one **Control tasks:** *Object memory:* Same as in OLM tasks but pairs of an encoded display and a display in which one of the objects had been replaced by a novel one were presented *Location perception:* Pairs of displays with three unique objects in three unique locations (ISI between displays: 0.75 s) were presented subsequently for 1 s (inter-pair interval: 2.25 s), twice in counterbalanced order. The displays were either the same or in one display the location of one of the objects had been changed. Participants had to indicate with button presses with the right hand whether the displays in a pair were identical or different *Object perception*: Same as location perception, but in altered displays one of the three objects had been replaced by a new one	**Behavioral:** **OLM tasks:** Young > old **Control task object memory**: Young > old **PET:** ANOVA of OLM and three control tasks with three factors: Type of processing (retrieval vs. perception), type of information (object or location) and group (young vs. old) Interaction age x type of processing x type of information: Retrieval OLM > retrieval object memory: Young: Right middle occipital gyrus Old: Tendency for left inferior frontal region

Note: OLM = Object-location memory. BDI = Beck Depression Inventory. CERAD = Consortium to Establish a Registry for Alzheimer's Disease. FAS = Word fluency with letters F, A, S. HAWIE-R = Hamburg Wechsler Intelligence Exam Revised Version. MAC-Q = Memory Assessment Clinics Questionnaire. MMSE = Mini Mental State Examination. MWT-B = Mehrfachwahl-Wortschatztest Version B. VBM = Voxel-based morphometry.

Meulenbroek and colleagues (2010) used the same fMRI paradigm as de Rover and colleagues (2008). Schiavetto and colleagues (2002) applied the same PET paradigm as Köhler and colleagues (1998a, b) with the adaptation that the object-location associations were presented three times during encoding for the young participants as in the original study, but for the older participants they were displayed five times. In addition, Kukolja and colleagues (2009) used the same paradigm as Cansino and colleagues (2002) with some timing modifications and 64 instead of 90 to-be-encoded object-location associations. Therefore, all age-comparative studies investigating brain regions specialized for OLM used computerized OLM paradigms with pictures of nameable everyday objects presented in grids or on the empty computer screen and assessed delayed OLM retrieval. Besides, the relations between the objects' locations were categorical and the OLM tasks mainly induced allocentric location processing.

During encoding, object-location associations were presented one after the other in the study by Kukolja and colleagues (2009), while Schiavetto and colleagues (2002) displayed several object-location associations simultaneously. Meulenbroek and colleagues (2010) applied both encoding conditions in their study. In the studies by Kukolja and colleagues (2009) and Meulenbroek and colleagues (2010), participants had to make artificial/natural decisions regarding the objects during encoding. They indicated their decisions by button presses.

Delayed OLM retrieval was assessed with cued recall using objects as retrieval cues in two studies (Kukolja et al., 2009; Meulenbroek et al., 2010), while it was tested in the remaining study (Schiavetto et al., 2002) with associative recognition. Responses were given in all studies by button presses. Brain activity due to motor responses was controlled for in all analyses with the exception of the study by Schiavetto and colleagues (2002) in which brain activity during OLM retrieval was contrasted with a visual fixation baseline.

Final sample sizes for both groups of young and older participants ranged from 12–20. Before conducting their final analyses, Kukolja and colleagues (2009) excluded eight older and three younger participants because of poor OLM retrieval performance as well as four young participants due to not enough falsely retrieved object-location associations. Concluding from the data provided by Kukolja and colleagues (2009) and Meulenbroek and colleagues (2010), the age ranges of the young and the older participants were 19–33 years and 52–77 years, respectively. Schiavetto and colleagues (2002) included a similarly aged young participant group, but their older participant group was slightly older. Sample sizes and gender distributions were approximately the same across the two experimental groups in all studies. They comprised roughly the same number of men and women in the studies by Kukolja and colleagues (2009) and Meulenbroek and colleagues (2010), whereas in Schiavetto and colleagues (2002) all participants were male with the exception of one older woman.

Inclusion criteria for the participants consisted of right-handedness verified by a questionnaire (Kukolja et al., 2009; Meulenbroek et al., 2010) and no history of neurological, medical, or psychiatric disorder in all three studies. In the study by Meulenbroek and colleagues (2010), the older participants were also excluded if they used psychopharmacological drugs, reported subjective memory problems, and did not have normal or corrected-to-normal vision. The last criterion applied also for participants of the study by Kukolja and colleagues (2009). In this study, no differences in education, depressive symptoms, verbal short-term memory, and verbal episodic memory were found between the young and the older participants. However, the older participants demonstrated higher crystallized intelligence and complained more about memory problems than the young participants, who in turn performed better than the older participants in a dementia screening as well as in a semantic and in a phonematic word fluency test. Anatomical differences

between the participant groups were also investigated. To this effect, voxel-based morphometry (VBM) analyses demonstrated significant greater gray matter volumes in the young compared to the older adults in insular, inferior prefrontal, superior parietal, and cerebellar cortices as well as in the bilateral fusiform gyrus. In addition, the older participants had greater gray matter volumes than the young participants in the right amygdala. However, the results regarding brain regions involved in OLM remained the same when age differences in gray matter volume were controlled for (Kukolja et al., 2009).

Generally, the older participants were outperformed by the young participants in all analyzed OLM tasks. Hence, in the study by Meulenbroek and colleagues (2010), OLM recall performance was included as covariate in the fMRI analyses. In addition, Kukolja and colleagues (2009) controlled for age differences in OLM performance by contrasting brain activity during encoding and retrieval of correctly retrieved object-location associations with brain activity during encoding and retrieval of incorrectly retrieved object-location associations.

Meulenbroek and colleagues (2010) conducted an ANOVA with age (young vs. older participants) as between-subject factor and OLM condition (all object-location associations simultaneously visible (first condition) and object-location associations presented sequentially during encoding (second condition)) as within-subject factor to assess the difference between brain activity during OLM retrieval and visual fixation baseline. They found a significant main effect of age, i.e., the older adults demonstrated increased brain activity in the left superior temporal lobe, the right putamen, the right insula, and the right caudate nucleus compared to the young adults, who in turn did not activate any brain regions more strongly than the older adults. Furthermore, there was no overlap between these brain regions and those found with the same contrast and same paradigm for the young participants in the study by de Rover and colleagues (2008), indicating that the older adults activated brain regions not

specifically involved in OLM. The additionally activated brain regions suggested that they might have drawn on supplementary language or motor processes to complete OLM retrieval. Moreover, the significant interaction between age and OLM retrieval condition revealed greater activity for the older than the young participants in the left middle temporal gyrus, the left inferior temporal gyrus/fusiform gyrus, the right parahippocampal gyrus, the right brain stem, the left internal capsule, the bilateral globus pallidus, and the bilateral thalamus during the retrieval of object-location associations which were shown simultaneously as compared to the retrieval of object-location associations which were presented sequentially during encoding. Again, the young adults did not activate any brain region more strongly than the older adults. The comparison of these findings to those of de Rover and colleagues (2008) and the other reviewed neuroimaging studies on brain regions involved in OLM in young adults demonstrates that in the first retrieval condition (simultaneously presented objects) with higher demands on OLM itself, the older adults activated regions generally implicated in OLM which may reflect their greater effort to successfully complete this task. In addition, the older adults activated brain regions (bilateral globus pallidus and thalamus) that de Rover and colleagues (2008) found to be associated with the presentation order of object-location associations during encoding as a cue for their later retrieval and as such with a strategy useful only for the second OLM retrieval condition (sequentially presented objects). This may indicate that the older participants had problems in switching between the different retrieval strategies induced by the two OLM retrieval conditions.

Schiavetto and colleagues (2002) reported greater brain activity in the young than the older participants in the right middle occipital gyrus and a tendency for increased brain activity in the older compared to the young participants in left inferior frontal regions during the retrieval of OLM compared to the retrieval of objects. In Köhler and colleagues (1998b), the young participants had additionally recruited the left lateral cerebellum during OLM

compared to object retrieval. Consequently, the results of Schiavetto and colleagues (2002) are in line with the PASA pattern (Davis et al., 2008) for age differences in brain activation during episodic memory tasks, revealing decreased activity in occipital regions accompanied by increased activity in frontal brain regions in the older compared to the young adults.

Finally, Kukolja and colleagues (2009) conducted ANOVAs on brain activity during OLM encoding and retrieval with age (young vs. older participants) as between-subject factor and retrieval success (correctly vs. incorrectly recalled object-location associations) as within-subject factor. For cued OLM recall, they found a significant main effect of age with greater activity in the left lateral superior parietal cortex in the young than the older participants and increased activity in the bilateral medial frontal gyrus, the left supplementary motor area, the bilateral inferior parietal cortex, the left middle temporal gyrus, the left anterior cingulate gyrus, and the left precuneus in the older compared to the young participants. In addition, there was a significant age x retrieval success interaction. During the retrieval of correctly vs. incorrectly recalled object-location associations, the young participants activated the left hippocampus more strongly than the older participants, who in turn did not activate any brain region to a greater extent. Generally, these findings indicate that – although the older participants recruited a far greater network of brain regions than the young participants during OLM retrieval – it did not help them to correctly recall encoded object-location associations. In addition, the recruitment of the left hippocampus may be essential for the better OLM retrieval performance of the young adults. Interestingly, there was some overlap between the brain regions that Cansino and colleagues (2002) found to be involved in correct as compared to incorrect OLM retrieval performance in the young participants and those specifically activated by the young and the older participants in the study by Kukolja and colleagues (2009) during OLM retrieval as well as during correct as compared to incorrect OLM retrieval. However, most of them were located in the contralateral hemisphere. For the older

adults, this corresponds to the HAROLD pattern (Cabeza, 2002), that is, the bilateral recruitment of brain regions as compared to the unilateral recruitment of these brain regions in the young adults. Also, the older adults generally activated frontal regions during OLM retrieval to a greater extent which is in line with the PASA pattern.

For OLM encoding, Kukolja and colleagues (2009) reported a significant main effect of age with greater brain activity in the young than in the older participants in the left fusiform gyrus and the left inferior occipital gyrus, whereas the older participants did not activate any brain region more strongly than the young participants. The interaction age x retrieval success was also significant and revealed increased activity in the left fusiform gyrus in the young compared to the older participants as well as increased activity in the older compared to the young participants in the right anterior cingulate gyrus for later correctly recalled vs. incorrectly recalled object-location associations. This indicates that the young adults recruited a brain region – the left fusiform gyrus – to a greater degree than the older adults during encoding which was relevant for later correct retrieval. The bilateral fusiform gyrus was also found to be involved in the encoding of later correctly recalled object-location associations in the young participants of the study by Cansino and colleagues (2002). Contrarily, the right anterior cingulate gyrus which was more activated in the older participants than in the young participants during the encoding of later correctly vs. incorrectly recalled object-location associations was not reported by Cansino and colleagues (2002) for this contrast. This brain region has been proposed to be a control region that proactively influences processing in effector regions to fulfill cognitive requirements (Weston, 2012) or to select the most relevant among currently available stimuli to guide behavior (Menon & Uddin, 2010). Thus, its specific activation in older adults may reflect their additional effort to encode object-location associations. Interestingly, the left anterior cingulate gyrus was generally activated to a

greater extent in the older compared to the young participants during OLM retrieval, suggesting similar attempts as during encoding.

In sum, both during OLM encoding and retrieval, the young adults demonstrated increased activity in relevant brain regions compared to the older adults, that is, the left fusiform gyrus during encoding and the left lateral superior parietal cortex, the left hippocampus, or the right middle occipital gyrus during retrieval. In contrast, the older adults activated brain regions that had not been involved in the young during OLM encoding and retrieval in the neuroimaging studies on this subject, or, if they had been involved, the brain regions were located in the contralateral hemisphere. Since these brain regions were mostly located in the frontal lobes, the findings are in line with the two major patterns of brain activation differences between young and older adults (PASA and HAROLD). Among the frontal regions, the anterior cingulate gyrus has most often been activated to a greater degree in older compared to young adults. In addition, the involvement of the left superior temporal lobe, the basal ganglia regions, and the thalamus indicates that the older adults may have drawn on differential strategies than the young adults to complete OLM encoding or retrieval (semantic or temporal order strategies).

3.4 Discussion

The purpose of this review was threefold: Firstly, to identify brain regions involved in intentional non-navigational episodic OLM by summarizing findings from lesion and functional neuroimaging studies, secondly, to indicate neural changes of OLM performance associated with advancing age, and thirdly, to discuss age-related OLM activation changes in the light of possible future interventions such as cognitive training.

The systematic literature search revealed 16 lesions studies as well as 12 functional neuroimaging studies with healthy young adults and three functional neuroimaging studies

comparing healthy young and healthy older adults with regard to brain regions involved in intentional non-navigational episodic OLM. Neither longitudinal studies investigating OLM activation changes across adulthood nor any relevant OLM training studies were found, thus revealing a clear research gap.

In the lesion studies, a wide range of OLM tasks was employed which differed with respect to the used material (computerized, paper-pencil, or real-world tasks), the spatial relations between the objects' locations (categorical or coordinate), and the used performance measures (encoding, immediate or delayed cued recall, or recognition). In contrast, in the functional neuroimaging studies, only computer paradigms assessing brain activity during encoding, delayed cued recall, or recognition of categorical OLM were applied. Among both types of studies, there were only a few that also manipulated the demands on egocentric versus allocentric location processing. Besides, in both lesion and neuroimaging studies, similar control tasks (object memory, location memory, or object-location perception) were included, however, the lesion studies implemented location memory as control task more often.

Methodologically, a great percentage of both lesion studies and functional neuroimaging studies with young adults did not report procedures for the verification of the health status of the included participants (both healthy and control participants). Contrarily, the functional neuroimaging studies on age differences employed adequate methods. Moreover, not all lesion studies screened their participants for important criteria such as handedness, perceptual deficits hindering OLM task completion, or brain damage besides the relevant lesions. In addition, the lesion studies frequently did not report if patient and control groups were matched with regard to relevant variables. In the functional neuroimaging studies on age differences in brain regions involved in OLM, the authors matched the younger and older participant groups more carefully for important variables. Furthermore, a

methodological weakness of the lesion studies comprised the small sample size of patient subgroups, thus posing a power problem for statistical analyses of group differences in OLM or control task performance. The functional neuroimaging studies had more adequate sample sizes.

Across the lesion studies, mainly patients with unilateral anterior and/or mediotemporal lesions were investigated. Only a few studies also included patients with lesions to other parts of the brain. In the studies with patients with unilateral anterior and/or mediotemporal lesions, the researchers established subgroups of patients in which varying amounts of the volume of the hippocampus, the surrounding parahippocampal gyrus, or the amygdala were affected in order to make conclusions about the specific involvement of these brain regions in OLM. However, these attempts were limited by the fact that the lesions of these patients could also extend to other anterior and/or mediotemporal regions. Moreover, most of the reviewed lesion studies included patients with epilepsy or patients with perinatal bilateral damage to the hippocampus which – as a consequence of early and long-lasting brain dysfunction – may have resulted in the functional reorganization of the brain.

Overall, the reviewed lesion studies point to specific roles of the hippocampus, the amygdala, and the parahipppocampal gyrus in coordinate and categorical OLM, with a tendency for a right-lateralization of these regions in coordinate OLM. In addition, there was some indication that bilateral parietal and occipital regions are important for coordinate and categorical OLM. Other anterior or mediotemporal brain regions may also be involved. Moreover, the findings from the lesion studies suggest that among the regions found to be involved in OLM, the right posterior parietal cortex and the right parahippocampal cortex may be particularly important for object-location perception. In contrast, bilateral parietal and occipital areas may be critical for object memory, whereas the right hippocampus may support all kinds of memory processes involved in OLM (object memory, location memory,

object-location binding) as well as allocentric processing of the objects' locations. Furthermore, coordinate OLM appears not to be dependent on subcortical brain regions and the frontal lobes seem to be involved in coordinate OLM tasks eliciting a high proactive interference only.

The neuroimaging studies with healthy young adults confirmed the special role of the parahippocampal gyrus and the posterior parietal cortex for categorical OLM. There was a tendency for a lateralization of these regions to the left during encoding and to the right during retrieval. In contrast to the lesion studies, there was only one study revealing an involvement of the right hippocampus and the right amygdala in categorical OLM. Instead, the inferior temporal gyrus/fusiform gyrus, the cerebellum as well as frontal and occipital regions were specifically activated during OLM encoding or retrieval. However, there was little overlap between activated frontal regions across the neuroimaging studies. Further, the involvement of occipital regions can be explained by the additional visual perceptual effort required for processing object-location associations in comparison to processing objects or locations alone. The neuroimaging studies with healthy young adults indicated a different specialization of the posterior parietal cortex, the parahippocampal gyrus, and the inferior temporal gyrus/fusiform gyrus with regard to OLM subprocesses. Accordingly, the posterior parietal cortex seems to be critical for location encoding and retrieval, the inferior temporal gyrus/fusiform gyrus for object encoding, and the parahippocampal gyrus for OLM retrieval. There was also some indication that the excitatory influence of the right posterior parietal cortex on the right fusiform gyrus increases during encoding. This might be the correlate of the object-location binding process. In addition, the bilateral posterior parietal cortex, the left parahippocampal gyrus, the left fusiform gyrus, and the right cerebellum have been found to be important for allocentric location processing.

The differences between the findings of the lesion and the functional neuroimaging studies with healthy young adults can be best attributed to the earlier discussed methodological differences between them. The functional neuroimaging studies seem to be methodologically superior with regard to the detection of non-mediotemporal brain regions involved in OLM and the specialization of these structures for subprocesses of OLM. However, they appear to have a lower sensitivity than the lesion studies for detecting mediotemporal regions involved in OLM because of magnetic susceptibility artifacts and their limited spatial resolution which does not allow to separate between the small mediotemporal subregions like the hippocampus and the surrounding parahippocampal tissue. Furthermore, the neuroimaging studies investigated solely categorical OLM with very specific computer paradigms, while the lesion studies implemented both coordinate and categorical OLM tasks with a great diversity in other task characteristics.

The synthesis of the reviewed studies confirms many of the proposals of the neurocognitive model of OLM by Postma and colleagues (2004, 2008) as discussed in the introduction. In particular, it approves the specialization of the inferior temporal gyrus/fusiform gyrus for object processing and that of the posterior parietal cortex for location processing. The lesion studies also support the proposal that the hippocampus predominantly supports object-location binding and allocentric location processing. In contrast, the neuroimaging studies indicate that the increased coupling between the activation of the posterior parietal cortex and the inferior temporal gyrus/fusiform gyrus during encoding and the activation of the parahippocampal gyrus during retrieval are the neural correlates of categorical object-location binding. Also, they did not find the hippocampus to be specialized for allocentric categorical OLM, but rather the bilateral posterior parietal cortex, the left parahippocampal gyrus, the left fusiform gyrus, and the right cerebellum. Moreover, the lesion studies support the suggested right-lateralization of regions involved in coordinate

OLM. However, both lesion and neuroimaging studies did not confirm the proposed left-lateralization of brain regions involved in categorical OLM. Finally, all reviewed studies implicate the importance of other anterior and/or mediotemporal (e.g., the amygdala), cerebellar, frontal, and occipital regions in OLM.

With regard to age differences in brain regions involved in OLM, the reviewed three neuroimaging studies indicate that older adults recruited relevant regions less strongly than young adults, that is, the left fusiform gyrus during encoding and particularly the left hippocampus during retrieval. Instead, they activated relevant brain regions to a greater degree in the contralateral hemisphere, or brain regions that had not been involved in OLM encoding and retrieval in the neuroimaging studies on this subject with young adults. Since the latter brain regions were mostly located in the frontal lobes, these findings are in line with the two major patterns of brain activation differences between young and older adults (PASA and HAROLD). Among the frontal regions, the anterior cingulate gyrus has most often been activated to a greater extent in the older than in the young adults. Further, the increased activity in the left superior temporal lobe, the basal ganglia regions, and the thalamus suggests that older adults might have drawn on differential strategies than young adults to complete OLM encoding or retrieval (semantic or temporal order strategies). However, the additional recruitment of brain regions and the use of other strategies seem to be inefficient since they performed worse than the young adults in the investigated OLM tasks.

Therefore, training targeting OLM in healthy older adults should enhance the activation of the left fusiform gyrus during encoding, the activation of the left hippocampus during retrieval, or attempt to suppress the application of inefficient strategies. Interestingly, the few studies on brain activation changes induced by episodic memory training demonstrated an increase in brain activity in the left fusiform gyrus (Kondo et al., 2005) in young adults or generally in occipito-parietal regions in young and older adults (Nyberg et al., 2003) after

instruction and practice of the method of loci. Moreover, Engvig and colleagues (2010, 2012) reported an increase in cortical thickness in the right fusiform gyrus and an increase in white matter integrity in major tracts of the left hemisphere (e.g., uncinate fasciculus, anterior thalamic radiation) after a similar training in older adults. Therefore, training the use of an efficient OLM encoding strategy might enhance the activation of the left fusiform gyrus in older adults. The study by Hampstead and colleagues (2012b) indicates that an efficient OLM encoding strategy is one that facilitates objet-location binding. Moreover, the findings of Noack and colleagues (2013) suggest that the recruitment of relevant brain regions in older adults may be improved by repeated practice of OLM tasks. Besides, anodal transcranial direct current stimulation (atDCS) over the right temporo-parietal cortex during OLM encoding may increase right hippocampal activation and thus OLM retrieval (Flöel et al., 2012). However, clearly more longitudinal studies are needed to gain a deeper understanding of the age-associated changes in brain regions involved in this type of memory and to enable the development of appropriate interventions to mitigate and potentially reverse its decline.

4 TRANSFER EFFECTS OF A PROCCESS-BASED OBJECT-LOCATION MEMORY TRAINING IN OLD AGE: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

4.1 Introduction

Object-location memory (OLM) is a subtype of spatial episodic memory and enables us to remember the locations of objects in our environment (Postma et al., 2008) such as keys or wallets in our houses, the parking spaces where we have left our cars, or the whereabouts of our favorite coffee shop two blocks away. These examples illustrate the relevance of OLM for daily-life functioning and thus how impaired OLM may hinder independent living and affect quality of life.

In fact, being unable to recall the locations of personal belongings is one of the most frequent memory complaints of healthy older adults (Bolla et al., 1991; Ossher et al., 2013). Subjectively experienced OLM impairments in old age have been corroborated by a number of studies demonstrating objective OLM deficits in older adults in both laboratory (e.g., Chalfonte & Johnson, 1996; Cherry & Park, 1993; Cooney & Arbuckle, 1997; Kessels et al., 2007; Kessels & Postma, 2006; Light & Zelinski, 1983; Park et al., 1990) as well as real-life settings (Caldwell & Masson, 2001; Uttl & Graf, 1993). Hence, there appears to be a great demand for tailor-made interventions that mitigate these impairments. Along these lines, cognitive training targeting OLM seems to be a particularly promising type of intervention since there is ample evidence for improvement of cognitive performance through cognitive training interventions in older adults (for reviews and meta-analyses see Eschen, 2012; Lustig et al., 2009; Martin et al., 2011; Verhaeghen et al., 1992).

Cognitive training aims to improve cognitive functioning by repeated practice of standardized cognitive tasks over a circumscribed timeframe (Gates & Valenzuela, 2010;

Martin et al., 2011; Rabipour & Raz, 2012). Different cognitive training approaches can be distinguished according to their underlying mechanisms. Strategy-based training stimulates the recruitment of additional or more efficient cognitive processes for task performance by teaching and practicing the use of strategies, whereas process-based training enhances the efficacy of task-inherent cognitive processes and induces their automation through repeated practice of the task with a performance-adaptive variation of task difficulty (Willis & Schaie, 2009). To date, episodic memory has been targeted mainly by strategy-based training. In contrast, process-based training extensively focused on several facets of executive processes (for a review see Kueider et al., 2012).

There is an ongoing debate about the faculty of cognitive training interventions to produce transfer effects, i.e., how they affect untrained cognitive abilities. Moreover, the lack of a generally valid definition of transfer distances – and thus arbitrary classifications of cognitive outcome measures assessing either near or far transfer – can be regarded as prominent causes for the so far inconclusive findings on training transfer. Hence, it is essential to carefully follow theoretical frameworks when planning to survey the transfer of a training regime to other cognitive domains (Papp et al., 2009). One such example is the taxonomy by Noack and colleagues (2009) whereby the scope of transfer to untrained tasks can be assessed with well-defined distances between trained and untrained abilities. Based on the hierarchical model of human intelligence by Carroll (1993), which classifies human cognitive abilities into narrow and broad abilities, Noack and colleagues (2009) defined transfer distance as near if training and transfer tasks assess the same narrow cognitive ability, as medium if outcome measures target a different narrow ability than the trained narrow ability, but all are from the same broad ability, and as far if training and transfer tasks measure abilities from different broad abilities.

Generally, the efficacy of a cognitive training intervention can be appraised by (1) the magnitude of gains in the trained cognitive ability, (2) the scope of transfer, and (3) the stability of training and transfer effects over time (Eschen, 2012; Eschen et al., 2012; Hertzog et al., 2008). Numerous studies have reported small to medium improvements in trained tasks after strategy-based training compared to passive control groups or control groups completing non-cognitive tasks (for meta-analyses see Gross et al., 2012; Martin et al. 2011; Verhaeghen et al., 1992). Furthermore, medium to large training gains induced by process-based performance-adaptive training have been demonstrated in older adults compared to passive or active control groups (for reviews and meta-analyses see Hindin & Zelinksi, 2012; Melby-Lervåg & Hulme, 2013; Morrison & Chein, 2011).

As already mentioned above, there are inconsistent findings on the scope of transfer of cognitive training. However, whereas strategy-based training has been found to yield mainly no or seldom transfer to untrained tasks (Lustig et al., 2009; Papp et al. 2009), for process-based training mostly near and even far transfer effects have been demonstrated (Hindin & Zelinksi, 2012; Melby-Lervåg & Hulme, 2013; Morrison & Chein, 2011; Shipstead et al., 2012).

Regarding long-term maintenance, training effects are evaluated by the slope of cognitive functioning from post-training to follow-up assessments months or years after the training. There is evidence that older adults were able to maintain training-induced increments in training and transfer task performance up to six years after training completion (Eschen, 2012; Lustig et al., 2009). However, only very few process-based training interventions have so far conducted longitudinal follow-up assessments.

To date, cognitive training studies not only differed in training approach, type and number of training tasks, frequency, or duration of training sessions but also in methodological features such as randomization procedure, blinding, and characteristics of

control groups (Martin et al., 2011; Rabipour & Raz, 2012). While the inclusion of passive control groups allows the control of retest effects in outcome measures, that of active control groups permits the additional control of unspecific influences of training participation itself on cognitive performance (being challenged by a cognitive intervention, receiving feedback, being in contact with study staff and other training participants, expectancy effects). Ideally, training interventions in both experimental and control groups should be as similar as possible to ensure that motivational and perceptual practice effects are reduced (for a review see von Bastian & Oberauer, 2014). Moreover, a double-blind controlled study design minimizes subjective expectancy effects and stratified randomization (e.g., by age or gender) ensures the balance of treatment groups with respect to critical variables. Hence, the aforementioned methodological discrepancies between previous cognitive training studies may account in part for the equivocal evidence regarding training efficacy, particularly in terms of transfer to untrained tasks.

Inconclusive evidence with regard to training efficacy may also be due to differences between training participants in variables such as age, personality traits, initial cognitive status, or motivation. Research investigating how these factors influence training efficacy is still scarce. Generally, younger age has been associated with larger training gains and greater transfer (Noack et al., 2013; Schmiedek, Lövdén, & Lindenberger, 2010; Verhaeghen et al., 1992; von Bastian & Oberauer, 2014). Furthermore, investigations on the relationship between cognitive performance at baseline and training gains yielded inconsistent results. Whereas in some studies larger training gains for individuals with low initial performance have been found (e.g., Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Karbach & Kray, 2009; Zinke, Zeintl, Eschen, Herzog, & Kliegel, 2011), others demonstrated increased improvement in training tasks for individuals with high initial cognitive status (e.g., Yesavage, Sheik, Friedman, & Tanke, 1990). In addition, higher educational attainment has been reported to

positively impact training gains (Langbaum, Rebok, Bandeen-Roche, & Carlson, 2009). Moreover, it has been demonstrated that conscientiousness and neuroticism influence training effects differentially, depending on the type of training intervention (Studer-Luethi, Jaeggi, Buschkuehl, & Perrig, 2012). Generally, a positive relationship between motivation and performance in cognitive tasks has been established (Hidi, 2006). There is first evidence that high training motivation leads to greater practice effects in older adults, although only small correlations between motivation and performance have been observed and solely at the individual and not at group level (Brose, Schmiedek, Lövdén, Molenaar, & Lindenberger, 2010).

To our knowledge, so far only two training interventions targeting OLM in older adults have been published. In a study by Hampstead and colleagues (2012a), cognitively healthy older adults and older patients with amnestic Mild Cognitive Impairment (aMCI) participated in three sessions of a strategy-based OLM training within two weeks and completed a similar OLM task with half trained and half untrained object-location associations – thus at best representing near transfer – before, immediately and one month after the training. Compared to an active control group who received the same training tasks but was not taught mnemonic strategies, both healthy participants and patients of the training group improved more in the outcome measure(s) from pre- to post-training (medium effect) as well as from pre-training to follow-up (large effect). Hence, the training effect appeared to increase over time since the follow-up effect size was larger than that immediately after training. The second study focused on practice-induced changes of OLM in younger and older adults (Noack et al., 2013). Younger and older participants practiced OLM intensively in 100 sessions. A fixed number of objects was serially presented in a 6x6-grid in random order. In addition to the locations, participants had to memorize the presentation order of the objects. While the presentation time of objects across training was assigned individually according to baseline

performance, the training was not performance-adaptive since the memory load and presentation time were held constant during the training period. Moreover, no control groups were included. Results confirmed that the older adults' performance in the training task improved significantly from pre- to post-training (medium effect size), but the younger adults gained more than the older adults (large effect size). In addition, while the younger participants improved memory for both location and order of objects, training gains of the older participants were limited to memory for location only (large effect size for OLM).

Although not investigating classical episodic OLM acquired by a glance at the environment from a static viewpoint but rather OLM acquired by spatial navigation through the environment, a third study is worth mentioning. In this study (Lövdén, Schaefer et al., 2012), healthy younger and older men performed a non-adaptive spatial navigation task every other day for four months. Results demonstrated that compared to an active control group (physical training) both younger and older training participants improved their training task performance to a greater degree (for younger and older adults large effects). At baseline, post and follow-up measurement points, participants were administered an extensive cognitive transfer battery consisting of 14 tasks measuring verbal and spatial episodic memory, working memory, mental rotation, perceptual speed, and reasoning. The interaction age x training group x time did not reach significance. However, improvements in the trained tasks were partly maintained four months after training termination although the effects declined in magnitude from post-training to follow-up.

Taken together, there is first evidence that OLM performance in older adults can be improved by strategy-based cognitive training targeting this ability and that these performance gains can be maintained for some time after training completion. In addition, there is some indication that strategy-based OLM training in healthy older adults can produce near transfer. However, so far we know very little about the efficacy of process-based OLM

training regimes that have participants practice OLM with a performance-adaptive variation in task difficulty in healthy older adults, particularly with regard to the scope of their transfer.

For this reason, the present study aims to explore a) the magnitude and course of OLM performance gains across 30 sessions of a process-based OLM training, b) the scope (near, medium, or large) and the temporal trajectory (from pre-training to the middle to the end of the training period) of transfer to untrained cognitive functions induced by this training, c) the persistence of these training effects up to four months after training completion, and d) the influence of individual differences on training gains.

In order to systematically control for factors potentially confounding the evaluation of training efficacy, we included an active control group participating in a visual perception training of similar duration, material, and structure as the OLM training. Moreover, we used adequate randomization and allocation concealment procedures (a double-blind design). The test battery for transfer assessments was chosen on theoretical grounds (Noack et al., 2009) to calculate composites from several cognitive tasks representing near (spatial associative episodic memory), medium (verbal memory), and far (reasoning) transfer. It was administered to both experimental and active control training groups at baseline, in the middle, and immediately after the training as well as four months later.

We hypothesized that OLM performance would increase linearly across the training period and that training effects would be medium to large (Hampstead et al., 2012a; Noack et al., 2013). Compared to the active control group, we expected OLM training participants to improve at least in near transfer performance during the training period. Moreover, near transfer effects would be largely maintained from post to follow-up measurement, i.e., there would be no significant decline. In addition, we anticipated training participants' characteristics, in particular motivational factors, to be positively associated with training success.

4.2 Methods

Design and procedure

The study was conducted as a randomized controlled double-blind trial with a two-group design, namely an experimental training group and an active control training group. Four measurement points were implemented in the course of the study: a baseline measurement before the training, an intermediate measurement after three weeks of training, a post measurement after six weeks of training, and a follow-up measurement four months after training completion. At all measurement points, participants completed a cognitive test battery in a 2.5 h-session and participated in a 1.5 h-neuroimaging session (including functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), and fluid-attenuated inversion recovery (FLAIR)) within the same week. The baseline measurement was preceded by a first screening phase in which potential participants filled out questionnaires at home assessing health and demographic variables, computer and internet experience, MRI safety requirements, personality traits (Körner et al., 2008), and handedness (Annett, 1970). This was followed by a second phase in which participants took part in a screening session of 1.5 h at the International Normal Aging and Imaging Center (INAPIC). After the baseline measurement, participants were invited to an individual training introductory session of 60 min in order to familiarize them with either the experimental or active control training. Due to limited scanner access, the study was conducted in three study waves over a time period of 18 months. Figure 2 provides an overview of study procedure and timeline.

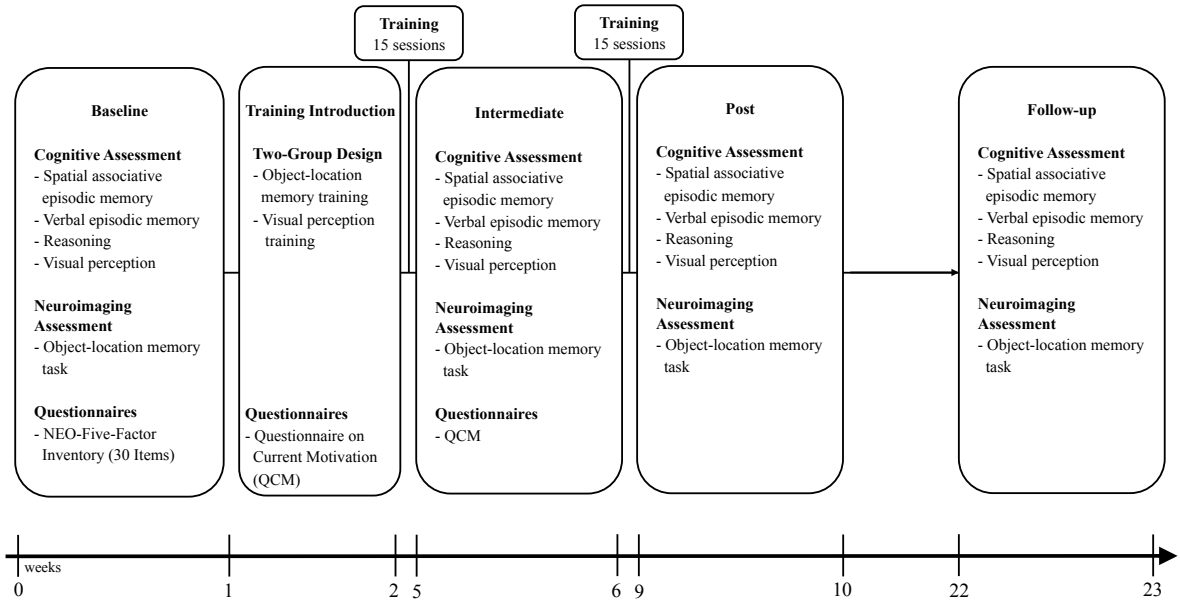

Figure 2. Study procedure and timeline in weeks.

Eligible participants were randomly assigned to either the experimental training group or the active control training group after baseline measurement. Randomization was accomplished according to the method of stratified randomization (Kang, Ragan, & Park, 2008) by study staff not involved in outcome assessments. Participants were stratified by study wave and gender. A restriction to the randomization was that a large enough number of the experimental training participants had to start the training a week before the active control participants because each of the latter was randomly matched to one experimental training participant. This matching algorithm ensured identical duration of training sessions of both training groups. In case of an experimental training participant dropping out, the matched active control participant had to be rematched to another experimental training participant. A participant with similar difficulty levels in all trained tasks was then chosen. Experimenters conducting outcome assessments were blinded to group allocation of study participants. The latter were also blinded with regard to their experimental group by informing them that the purpose of the study was to examine the efficacy of different types of memory training. Moreover, they were urged not to exchange information about their training regime among

each other when meeting in group sessions of cognitive transfer assessments.

While participants of the experimental training group trained OLM, the active control group completed visual perception tasks. Visual perception was chosen as the target cognitive function of the control training because it represents a function of a different broad ability according to the hierarchical model of human cognitive abilities by Carroll (1993) and does not require memory capacity. To ensure identical training conditions between participants of both training groups, the two training programs were computerized, comprised the same stimulus material, had a similar structure, and were matched in duration. Training was accessible from participants' home via the open-source software Tatool (von Bastian, Locher, & Ruflin, 2013). It included 30 sessions, divided into two training blocks of 15 sessions each, with a break of one week in between. Both groups trained three different tasks which were presented in randomized but counterbalanced order across participants.

In order to assess transfer effects, five spatial associative episodic memory tasks for near transfer, three verbal episodic memory tasks for medium transfer, and six reasoning tasks for far transfer were employed. Reasoning was chosen from other possible far transfer abilities because drawing conclusions requires forming and retrieving associations between different information units. In addition, to evaluate possible near transfer effects of the visual perception control training, three visual perception tasks were implemented which differed in stimulus material and test format from the training tasks. The cognitive tests were conducted in groups of one to four participants.

The study was approved by the Ethics Committee of the Canton of Zurich.

Participants

Participants were recruited at lectures for senior citizens at the University of Zurich, through newspaper articles, advertisements in magazines, public talks, flyers, and word of mouth. All participants gave written informed consent. They received 320 CHF (approx. 340 USD) for their participation in the study. Inclusion criteria were age between 60–75 years, right-handedness, native German speaker or fluent in German, basic computer and internet experience, and access to a computer as well as the internet during the training period. Exclusion criteria were history of previous or current neurological and psychiatric disorders or substance use negatively affecting brain function, sensory and motor deficiencies hindering conduction of training and outcome measurements, violation of MRI safety requirements, and participation in a training study within the last five years. In addition, participants who scored 1.5 *SD* below age-, gender-, and education-specific norms in more than one subtest of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-NAB; Berres, Monsch, & Bernasconi, 2000) or had a sum score > 5 in the short version of the Geriatric Depression Scale (GDS; Sheik & Yesavage, 1986) were excluded from study participation.

Details of the recruitment process and reasons for excluding participants from study participation can be seen in Figure 3. Eight individuals had to be excluded from the study. Reasons included failed screening tests, incidental findings, or claustrophobia detected at baseline neuroimaging transfer assessment. A total of 51 participants completed the study, 27 participants of the experimental training group and 24 participants of the active control group (32 women, 19 men; M_{age} = 67. 42, *SD* = 3.96, age range 60–75 years). Overall, participants were highly educated and demonstrated high IQ scores, no signs of clinical depression, and age average screening scores.

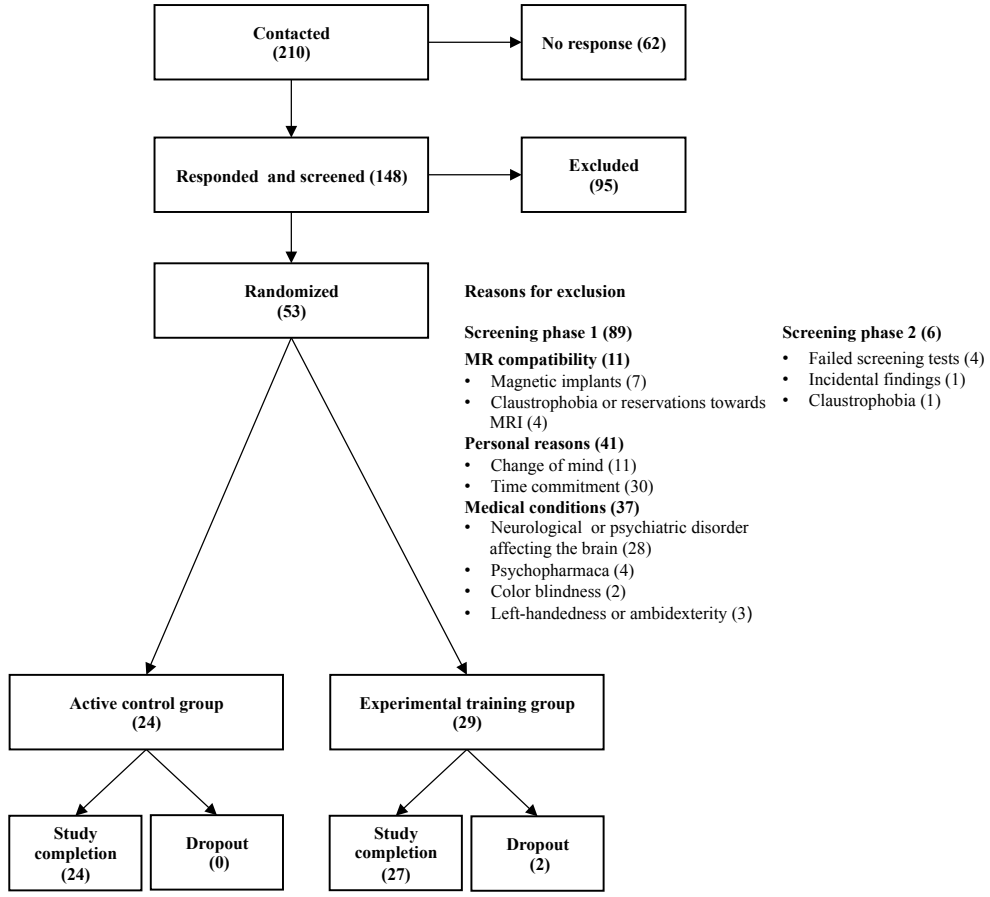

Figure 3. Recruitment process and reasons for excluding participants from study participation.

4.3 Material

Screening session measures

Cognitive deficits. With the CERAD-NAB test battery (Berres et al., 2000), participants were tested for cognitive deficits indicative of Mild Cognitive Impairment (MCI) or dementia. The test battery includes the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), a semantic fluency test, a short version of the Boston Naming Test with 15 items, a constructional praxia test, a visual delayed free recall test, a 10-word list learning test, immediate and delayed free recall as well as a discrimination test of this word list. Participants who scored 1.5 *SD* below age-, gender-, and education-specific norms in more than one subtest were excluded from study participation. One participant was very nervous during CERAD assessment and failed two subtests (i.e., delayed recall of constructional

praxia and delayed recognition of wordlist). Because of his nervousness, we decided to administer an additional screening test for delayed recall of figural material, i.e., the more complex Rey-Osterrieth Complex Figure Test (Osterrieth, 1944; Rey, 1941) and another screening test for delayed recognition of a wordlist (NAI; Oswald & Felischmann, 1997). In both tests he demonstrated performances 1.5 *SD* above age-specific norms.

Crystallized intelligence. The 37 items of Spot-a-Word (MWT-B; Lehrl, 1977) comprise each one word and four pronounceable nonwords which are similarly spelled or similarly sounding. Participants were asked to mark the word among the nonwords. Scores are IQ values deducted from the sum of correct responses (possible range: 0–37).

Depression. The short version of the Geriatric Depression Scale (GDS; Sheik & Yesavage, 1986) screens with 15 items for clinically relevant depressive episodes in older individuals. Cut-off score is 5, i.e., higher scores are indicative of potential clinically relevant depressive episodes.

Training

At the beginning of each training session, participants declared their current emotional state on two 9-point Likert scales which were illustrated with Self-Assessment-Manikin (Bradley & Lang, 1994) as well as their current training motivation on a 5-point Likert scale. Furthermore, they were asked if any special event had occurred since the last training session.

Experimental training

Participants assigned to the experimental training group solved three OLM tasks: a shape-location task, a landmark-location task, and an object-location task. The training of all tasks allowed individualized performance-adaptive progression of difficulty level which was defined by the number of to-be-encoded object-location associations and increased by one

association from one difficulty level to the next higher. The lowest difficulty level comprised two stimuli and was given in the first training session. A total of 20 difficulty levels for each task was provided. If participants reached a performance accuracy above 70% in a training task in one training session, they had to complete the next higher difficulty level in this training task in the next training session. If they reached a performance accuracy between 50–70% in a training task in one training session, the difficulty level remained the same in this task in the next training session, and if performance accuracy was below 50%, participants trained in a lower difficulty level in this training task in the next training session.

All tasks included an encoding, a distractor, and a retrieval phase and consisted of 10 trials each. Prior to all three training tasks, a practice trial of the easiest difficulty level was available. This trial could be worked through or skipped. Mean task completion time varied from 11.76 min in session 1 (*SD* = 2.22; range 9.33–18.67) to 17.11 min (*SD* = 4.90; range 9.67–27.67) in session 30. Figure 4 provides one trial of each of the three OLM training tasks.

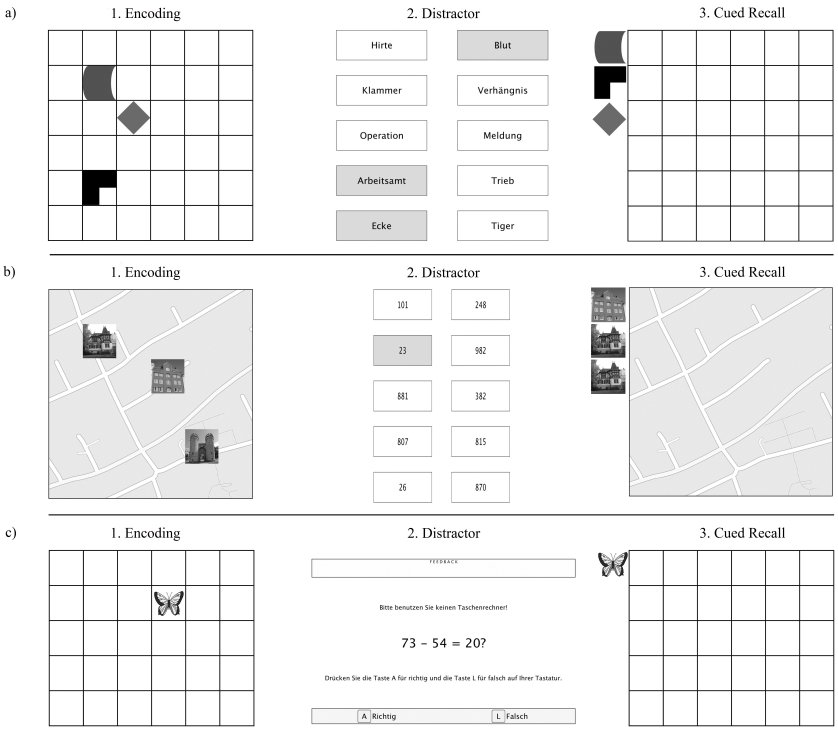

Figure 4. Exemplary trials of the three training tasks a) shape-location task, b) landmark-location task, and c) object-location task.

A database of 261 self-created shapes (29 different geometrical shapes in nine colors) was available for the shape-location task. For the landmark-location task, 261 photographs of non-famous buildings retrieved from several websites were provided (see supplementary material). In addition, stimuli for the object-location task were drawn from a database of 245 colored drawings of everyday objects (Rossion & Pourtois, 2004; Snodgrass & Vanderwart, 1980). In each of the 10 trials of the three training tasks, different shapes, photographs of buildings, or everyday objects were presented during a training session.

Encoding phases. During the encoding phases of the shape-location task and the landmark-location task, 2–21 stimuli (shapes and buildings, respectively) were presented simultaneously for 6–63 s in a 6x6-grid. For the landmark-location task, the grid was superimposed by a different fictitious city map in each training session and the hidden gridlines were thus not applicable as reference frames. In the object-location task, 2–21 objects were presented serially in a 5x6-grid for 4 s each with interstimulus intervals (ISIs) of 0.5 s. Locations of stimuli were randomly allocated across the 10 trials of the training tasks in each session. However, slightly overlapping locations of the to-be-encoded stimuli across trials were unavoidable.

Distractor phases. The encoding phases were followed by subsequent distractor phases, each lasting for 20 s. For the shape-location task, 10 words had to be clicked on with the computer mouse in alphabetical order, for the landmark-location task, 10 two-digit numbers had to be clicked on in order of their magnitude, and for the object-location task, serially presented simple arithmetic calculations had to be evaluated with respect to their accuracy. After each distractor trial, participants received feedback regarding their performance.

Retrieval phases. During the retrieval phases of the shape-location and the landmark-location task, previously presented empty grids or maps were displayed with the encoded 2–21 stimuli on the left side, and participants had to relocate them to their correct positions by

mouse click (duration 12–126 s). The retrieval phase of the object-location task consisted of 2–21 serially presented stimuli which had to be relocated to their correct positions with mouse clicks one at a time. Each object was presented for a maximum of 6 s. Then or after an earlier mouse click, the next object was presented for relocation (total duration 12–126 s).

Feedback. At the end of each training task trial participants received feedback about the number and percentage of correctly relocated objects. In addition, after each training task, the percentage of correctly recalled stimuli in all 10 trials and the level of difficulty on which participants had trained as well as the difficulty level of the same task in the next training session were presented. At the end of each session, separate graphs for each training task appeared on the screen which displayed the graphical trend of performance and reached difficulty level in each task across the 10 trials of the session.

Control training

The trials of each perception training task were divided into a first perception phase, followed by a distractor phase and a second perception phase. The perception phases were equal in duration to the encoding and retrieval phases of the corresponding training task in the same training session of the individually matched participant of the experimental training group. Mean task completion time varied from 11.49 min (*SD* = 1.66; range 10.00–17.33) in session 1 to 14.01 min (*SD* = 3.19; range 10.00–20.00) in session 30. The group x time interaction was not significant, thus indicating that the durations of both training regimes did not develop differently across the 30 training sessions ($F(29, 21) = 0.803$; $p > .05$).

Shape perception task. A 6x6-grid filled with 36 different shapes randomly drawn from the same database employed for the shape-location task was presented. Above the grid, a target shape was displayed which participants had to indicate as quickly as possible within the grid by mouse click. Subsequently, a new grid was shown.

Landmark perception task. This task was identical to the shape perception task but comprised an additional fictitious map superimposed on the 6x6-grid which contained 21 photographs of buildings. Again, a target stimulus was presented above the map and had to be found within the map as quickly as possible and indicated by mouse click.

Object perception task. Participants were presented two 1x10-grids filled with objects, one above the other. The bottom grid differed from the upper grid in one of the 10 objects. Participants had to indicate this target object as quickly as possible by mouse click.

Feedback. After each training task trial, participants received immediate feedback regarding performance accuracy and average reaction time for one target-choice comparison. For each completed training task, the number and the percentage of correctly executed target-choice comparisons and the mean reaction time across all 10 trials were given. Finally, at the end of each training session, graphs containing the mean reaction time across the 10 trials of each of the tasks were provided. Figure 5 displays one trial of each control training task.

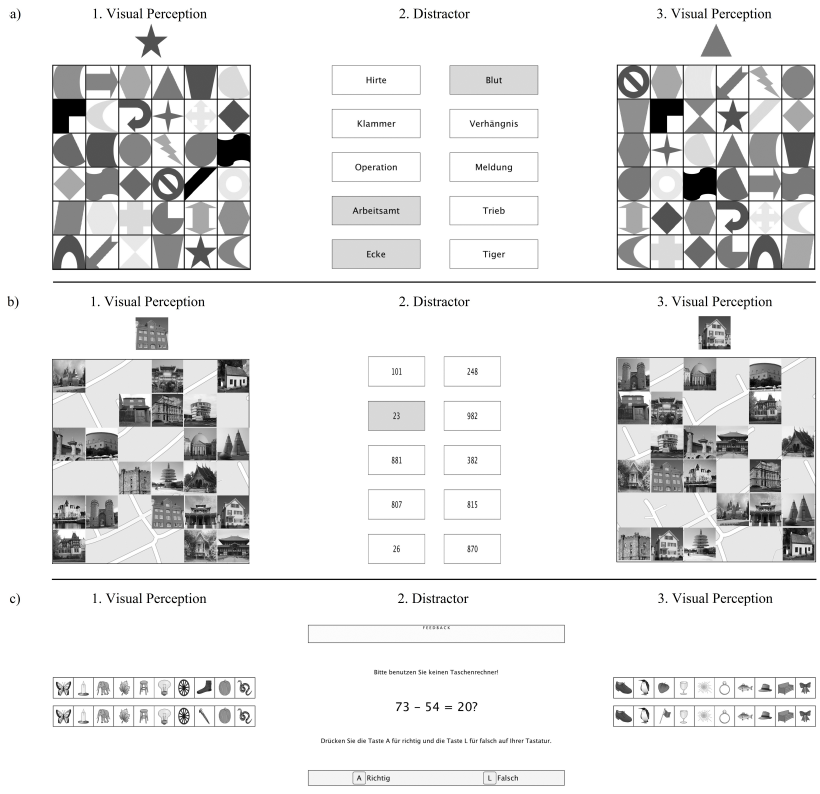

Figure 5. Exemplary trials of the three active control training tasks a) shape-perception task, b) landmark-perception task, and c) object-perception task.

Transfer

Near transfer: *spatial associative episodic memory*

For near transfer, five tasks were selected which required forming and retrieving visuo-spatial associations similar to the experimental training tasks but were of different material and test format. From the paper-and-pencil Berlin Intelligence Structure Test Form 4 (BIS-4; Jäger, Süss, & Beauducel, 1997), the three subtests measuring spatial associative episodic memory were used, i.e., the Orientation Memory Task, the Remembering Route Task, and the Company Sign Task.

In the Orientation Memory Task, 27 black buildings on a city map had to be encoded within 90 s. In the subsequent retrieval phase of 90 s, the encoded black buildings had to be marked on an uncolored copy of the map.

In the Remembering Route Task, participants had to memorize within 30 s the marked route from one place to another on a stylized map with shaded geometrical shapes denoting blocks of buildings. During immediate retrieval, participants had to reproduce the route on a copy of the map without this route within 40 s.

In the Company Sign Task, participants were asked to encode differently shaped frames around 20 company signs consisting of objects, letters, or abstract shapes within 60 s. During subsequent retrieval, each of the company signs was presented with four different shapes below, and participants had to indicate within 90 s which of the shapes had framed the company picture during encoding.

The OLM Pairs Task was computerized and based on a memory task developed by Rasch, Büchel, Gais, and Born (2007). Participants had to encode 15 pairs of real-world objects in a 5x6-grid. The first object was presented for 1 s immediately followed by the second object of the pair. Both objects were visible for 3 s. After an ISI of 3 s, the first object of the next pair appeared in the grid. The following distractor task comprised an adapted

version of the Letter Digit Substitution subtest of the HAWIE-R (Tewes, 1991) and lasted 30 s. During subsequent retrieval, one object of the pair was presented and the location of the second object had to be indicated by mouse click. Irrespective of whether an answer had been given or not, the second object was presented in its correct location after 4 s. The pair was shown for 2 s and again, after an ISI of 3 s, the first object of the next pair was presented. The OLM Pairs Task was conducted twice.

The fMRI OLM Task used in neuroimaging assessments served as fifth near transfer task. In each of the 12 trials of the two conducted runs, participants first had to encode six objects which were presented serially in a 5x5-grid for 3 s each (ISI = 0 s). The subsequent distractor task lasted for 12–18 s and consisted of a 1-back task of serially presented arrows which could point in one of eight directions. Participants had to indicate with button presses if two consecutively shown arrows were equal or not. Each arrow was shown for 1 s (ISI = 1 s). During the following forced-choice recognition, the six encoded objects were shown sequentially for 3 s each in the grid (ISI = 0 s). Three objects were presented in the same locations as during encoding, the other three objects in different locations. Participants had to indicate with button presses whether the same object-location associations as during encoding were presented or not. Then, a black fixation cross appeared on the screen for 9–15 s. It turned green for the last 2 s to announce the beginning of the next trial.

Medium transfer: verbal episodic memory

For medium transfer, in which training and transfer tasks target the same broad but a different narrow ability, three subtests from the BIS-4 were selected which all measure verbal episodic memory (Jäger et al., 1997).

In the Meaningful Text Task, participants were asked to encode a text for 60 s. During immediate retrieval, they had to write down answers to detailed questions about the text

within 120 s.

In the Remembering Words Task, a list of 20 words (both concrete and abstract) had to be memorized within 40 s and then immediately recalled in written form within 90 s.

In the Fantasy Language Task, 20 word-pairs had to be encoded for 60 s. Each word-pair consisted of one real word and one nonsense word. During the subsequent retrieval (lasting 75 s), five nonsense words were presented for each encoded real word, and the nonsense word which had been associated with the real word during encoding had to be marked.

Far transfer: reasoning

To assess far transfer, in which training and transfer tasks measure different broad cognitive abilities, the five visuo-spatial reasoning subtasks from the BIS-4 were chosen (Jäger et al., 1997).

In the Analogies Task, two abstract shapes were presented next to each other in each of the eight items. Participants had to figure out how they relate to each other and apply the same relationship to a second pair of shapes. Of this pair, the first shape was given and the second shape had to be selected among five choices. Task duration was 105 s.

In the Charkov Task, 1x6-grids were presented. In the first cell, a pattern was drawn which continued over the next three cells. For all six items, participants had to complete the pattern in two succeeding cells. Task duration was 180 s.

In the Bongard Task, two groups of six spatial arrangements consisting of triangles and dots were presented. During 130 s, participants were asked to decipher in five items the logical relations among the spatial arrangements of the two groups and to allocate three additional arrangements to one of the two groups.

In each of the six items of the Shape Selection Task, three to four pieces of a larger

shape were presented in a random distribution. Participants had to find out which of five presented larger shapes could be built from these given pieces. Task duration was 150 s.

The Transaction Task consisted of five items in which participants were asked to select the correct three-dimensional figure out of five choices after having mentally assembled the displayed folding template. Task duration was 110 s.

Finally, the short form of the Raven's Advanced Progressive Matrices (Arthur & Day, 1994) with 12 items was employed. For each item, participants were asked to choose one out of eight alternative pieces that completed a figure with a missing piece according to a certain logical principle. No time restraints were given in this task.

Control tasks: visual perception

To examine visual discrimination skills, we selected the three paper-and-pencil tasks representing the cognitive factor perceptual speed from the Kit of Factor-Referenced Cognitive Tests (Ekstrom, French, Harman, & Dermen, 1976). The items in all three tests were displayed in closely spaced arrays to ensure that participants had to visually discriminate between the stimuli.

In the Finding A's Test, as many words containing the letter 'a' as possible had to be marked in two trials of 120 s each.

In the Number Comparison Test, pairs of 3- to 12-digit numbers had to be compared as quickly as possible and marked when different in two trials of 90 s.

The Identical Pictures Test incorporated a match-to-target paradigm. The black and white target picture had to be indicated as quickly as possible among five options in two trials of 90 s each.

The scores of all transfer tasks represented the number of correctly solved items.

Self-report measures

Personality traits. During the first screening phase, participants completed the German 30-item short version of the NEO-FFI (Personality Assessment with the NEO-Five-Factor Inventory; Körner et al., 2008) which includes the scales neuroticism, extraversion, openess to experience, agreeableness, and conscientiousness. The six items of each scale have to be rated on a 5-point Likert scale (0 = does not apply; 4 = applies exactly). From these ratings, sum scores are computed. The subscales have a good internal consistency (Cronbach's alpha .67 to .81) and are highly correlated with the original NEO-FFI scales (Körner et al., 2008).

Motivation. The German Questionnaire on Current Motivation (QCM; Rheinberg, Vollmeyer, & Burns, 2001) assesses current motivation towards learning situations. The items of the questionnaire are adapted to represent the respective learning situations, in our study the participation in a cognitive training. The questionnaire consists of four factors, i.e., interest in, expected success in, challenge by, and anxiety towards the learning situation. The 18 items have to be judged on a 7-point Likert scale (1 = does not apply; 7 = applies exactly). From the ratings of the relevant items, sum scores for the four subscales are computed. Varying internal consistencies (Cronbach's alpha .66 to .90) have been measured in six samples (N = 944). In addition, the questionnaire's validity has been supported by findings of studies in which initial motivational factors were related to subsequent learning behaviors as well as outcomes (Rheinberg et al., 2001). In the present study, participants were asked to complete the questionnaire at both baseline and intermediate measurement points.

4.4 Analyses

Analyses were conducted using SPSS20 (http://www.spss.com) and MATLAB R2013b (Mathworks Inc., MA, USA). Alpha level was set at .05 for all analyses. Effect sizes of analyses of variance ((M)ANOVAs) are partial eta-square values.

We identified outliers in our transfer data by the median absolute deviation (MAD) and replaced them with the median of the raw scores plus or minus three MADs (for calculation of MAD, see Leys, Ley, Klein, Bernard, & Licata, 2013).

Composites for near, medium, and far transfer as well as for the visual perception control measure were computed by first *z*-standardizing the raw data of all cognitive outcome tests with respect to the means and standard deviations of the whole sample at baseline measurement. Due to no variability at the first measurement point, one far transfer task, the Charkov Task, was excluded. To ensure that the remaining cognitive outcome tasks could be merged into composite scores of their envisaged transfer distance and the control measure, we computed a first explorative factor analysis (principal component analysis with orthogonal rotation) which yielded five factors with Eigenvalues above Kaisers's criterion of 1. Four tasks (the Company Sign Task for near transfer, the Fantasy Language Task for medium transfer, the Shape Selection Task and the Transaction Task for far transfer) loaded similarly high on two to three factors and thus were removed. A new factor analysis was conducted with the remaining 12 cognitive outcome tasks. The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis (KMO = .514). Bartlett's test of sphericity indicated that correlations between individual tests were sufficiently large ($\chi^2(66) = 116.14$; $p < .001$). Furthermore, four factors with Eigenvalues above Kaiser's criterion of 1 were identified and explained in combination 60.01 % of the variance. The first factor represented spatial associative episodic memory with four tasks (Remembering Route Task, Orientation Memory Task, OLM Pairs Task, fMRI OLM Task), the second factor verbal episodic memory with two tasks (Meaningful Text Task, Remembering Words Task), the third factor reasoning with three tasks (Analogies Task, Bongard Task, Raven's Advanced Progressive Matrices), and the fourth factor visual perception also with three tasks (Finding A's Test, Number Comparison Test, Identical Pictures Test). Hence, all tests were assigned to the envisaged composite and

comprised rotated factor loadings above 0.56. The *z*-standardized test scores of each factor were averaged to yield the final near, medium, far transfer as well as control task composites.

Training and transfer assessments were completed by all 51 participants with the exception of one participant of the experimental training group who – due to medical reasons – did not take part in follow-up testing. However, the three completed cognitive assessments of this participant were included in the analyses. Because of technical software problems, two participants of the active control group completed 29 and one participant only 28 sessions. Of the experimental training group, one participant completed 27 and another participant 29 instead of the planned 30 training sessions. For these two individuals, the difficulty levels of the missing training sessions were interpolated based on their precedent training progression. Furthermore, to maximize power, we included all 51 participants in the analyses assessing training gains, transfer, and contributions of individual differences to training effects. Along these lines, data was checked for assumptions of normal distribution, sphericity, univariate and multivariate normality for dependent variables as well as for equality of covariance matrices.

4.5 Results

Comparison of experimental groups for demographics and screening variables

We conducted a MANOVA with group (experimental training group, active control group) as between-subject factor and demographic characteristics and screening measures as dependent variables which demonstrated no significant differences between the two groups ($F(14, 36) = 0.440$; $p > .05$). Overall, the study sample comprised more women than men, however the gender distribution did not significantly differ between both training groups ($\chi^2(1) = 0.001$; $p > .05$). Table 4 displays characteristics and initial screening measures of study participants.

Table 4. Demographic characteristics and initial screening measures of study participants at baseline

	Experimental training group (*n* = 27) *M* (*SD*); range	**Active control training group (*n* = 24)** *M* (*SD*); range	**Total (*N* = 51)** *M* (*SD*); range
Demographics			
Age	67.11 (4.11); 60–75	67.75 (3.85); 61–75	67.42 (3.96); 60–75
Gender (male: *n* (%) / female: *n* (%))	10 (37.0%) / 17 (63.0%)	9 (37.5%) / 15 (62.5%)	19 (37.3%) / 32 (62.7%)
Education in years	15.19 (3.54); 9–24	13.88 (3.17); 10–20	14.57 (3.40); 9–24
Computer experience in years	18.35 (8.35); 2–45	17.92 (7.17); 4–32	18.15 (7.74); 2–45
Internet experience in years	12.38 (6.42); 0.83–25	11.63 (5.50); 4–25	12.02 (5.96); 0.83–25
Screening measures			
CERAD (in *z*-values)			
Verbal fluency	0.14 (0.72); -1.17–1.43	0.24 (0.80); -1.76–1.42	0.19 (0.75); -1.76–1.43
Boston naming test	0.65 (0.64); -0.73–1.74	0.97 (0.49); -0.65–1.58	0.80 (0.59); -0.73–1.74
Immediate free recall of wordlist (total score)	0.67 (0.91); -0.86–2.62	0.60 (0.91); -1.03–2.21	0.63 (0.90); -1.03–2.62
Delayed free recall of wordlist	0.43 (0.93); -1.10–1.89	0.30 (1.00); -1.42–1.85	0.37 (0.95); -1.42–1.89
Delayed recognition of wordlist (discrimination score)	0.22 (0.79); -2.25–1.03	0.25 (0.71); -1.37–0.97	0.24 (0.75); -2.25–1.03
Constructional praxia	0.48 (0.61); -1.47–1.43	0.46 (0.79); -1.50–1.41	0.47 (0.69); -1.50–1.43
Delayed free recall of constructional praxia	0.43 (1.19); -2.11–2.22	0.39 (1.11); -1.47–1.94	0.41(1.14); -2.11–2.22
MMSE (in score points)	29.15 (0.77); 28–30	29.42 (0.72); 28–30	29.27 (0.75); 28–30
MWT-B (in IQ values)	123.56 (10.53); 104–136	124.63 (11.13); 104–145	124.06 (10.72), 104–145
GDS short form (0–15; normal < 5)	0.52 (0.75); 0–3	0.78 (1.24); 0–4	0.65 (1.00); 0–4

Note: CERAD-NAB = Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery. MMSE = Mini Mental Status Examination. MWT-B = Mehrfachwahlwortschatztest B. GDS =Geriatric Depression Scale.

Training motivation

To assess possible differences in training motivation between the two training groups, a mixed 2x2 MANOVA with group as between-subject factor (experimental training group, active control group) and time (baseline, intermediate measurement points) as within-subject factor was conducted. Dependent variables were the four scales of the Questionnaire on Current Motivation (QCM; Rheinberg et al. 2001), i.e., interest, expected success, challenge, and anxiety towards the cognitive training. Results indicated no difference with respect to motivational factors between the two training groups ($F(4, 46) = 1.855$; $p > .05$) as well as no group x time interaction ($F(4, 46) = 1.092$; $p > .05$). The main effect of time was significant ($F(4, 46) = 5.825$; $p < .01$) indicating that motivational factors of both groups were similarly affected by time.

Training gains

To analyze the trajectory of performance in the experimental training tasks across the 30 training sessions, polynomial contrasts involving time were used. A significant positive linear trend for all three training tasks was found, indicating that experimental group means for all tasks increased linearly across all training sessions (shape-location task: $F(1,26) = 52.761$; $p < .001$; $\eta p^2 = .670$; landmark-location task: $F(1,26) = 30.099$; $p < .001$; $\eta p^2 = .537$; object-location task $F(1,26) = 60.771$; $p < .001$; $\eta p^2 = .700$). The magnitude for the observed effect was largest for the object-location training task and smallest for the landmark-location training task, however, according to Cohen (1988), the effects were large for all training tasks.

Furthermore, we conducted a repeated measure ANOVA with time (baseline, intermediate, post) as within-subject factor to investigate whether the mean training gains between training session 1 (baseline) and training session 15 (intermediate) as well as between training session 15 and training session 30 (post) were similar. Results indicated that

the assumption of sphericity for all three tasks had been violated (all *p*s < .05), hence Greenhouse Geisser estimates are reported. For all training tasks, improvements were significantly affected by time (shape-location task: $F(1.33, 34.54) = 45.46$; $p < .001$; $\eta p^2 = .636$; landmark-location task: $F(1.16, 30.17) = 27.70$; $p < .001$; $\eta p^2 = .516$, and object-location task: $F(1.27, 32.88) = 53.60$; $p < .001$; $\eta p^2 = .673$). Effect sizes for all tasks can be considered large (Cohen, 1988). Follow-up contrast analyses confirmed that the mean magnitude of performance increase was equally large between session 1 and session 15 ($F(1, 26) = 58.587$; $p < .001$; $\eta p^2 = .693$) as well as between session 15 and session 30 ($F(1, 26) = 43.151$; $p < .001$; $\eta p^2 = .624$). Figure 6 displays the mean performance of the experimental training group in each of the 30 sessions of the three experimental training tasks.

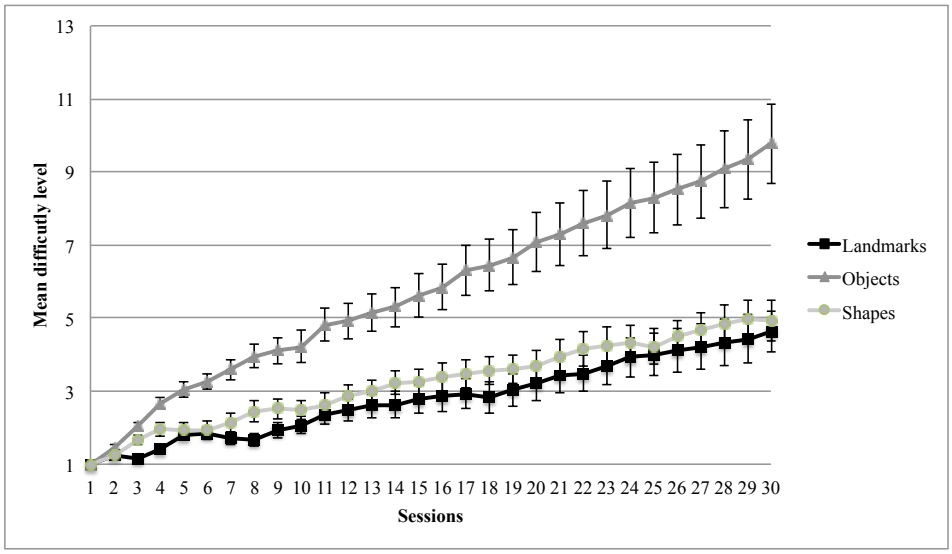

Figure 6. Mean performance of the experimental training group in three training tasks for all 30 sessions. Error bars represent standard errors of the mean.

Training transfer

A 2x4 MANOVA with group as between-subject factor (experimental training group, active control group) and the four composites as dependent variables revealed that the two training groups did not differ at baseline with respect to transfer and control measures ($F(9, 40) = 1.719$; $p > .05$). Therefore, the found effects can be interpreted as training-induced rather than being based on baseline differences.

For the detection of possible training effects on untrained tasks, we used a mixed 2x4 MANOVA with group as between-subject factor and time (baseline, intermediate, post, follow-up measurement points) as within-subject factor. The main effect of group was not significant, however, the main effect of time ($F(9, 432) = 15.846$; $p < .001$; $\eta p^2 = .248$) as well as the group x time interaction ($F(9, 432) = 1.923$; $p < .05$; $\eta p^2 = .039$) were significant, indicating that the experimental and control training regimes had different effects on performance across all transfer distances. Univariate tests showed also a significant main effect of time for all composites (all Fs$(1, 144) > 5.971$; all ps $< .01$). Contrary to all other transfer distances (all Fs$(3, 144) < 0.893$; all ps $> .05$), we observed a significant group x time interaction ($F(3, 144) = 4.981$; $p < .01$; $\eta p^2 = .094$) for near transfer. The experimental training resulted in significantly larger improvements across time compared to the active control training. According to Cohen (1988) this effect can be considered medium.

Finally, to test how the two training regimes affected performance in the visual perception control composite across time, we computed a mixed 2x4 ANOVA with group (experimental training group, active control group) as between-subject factor and time (baseline, intermediate, post, follow-up measurement points) as within-subject factor. Results indicated neither a difference between the two training groups ($F(1, 48) = 0.205$; $p > .05$) nor a group x time interaction ($F(3, 46) = 0.750$; $p > .05$). The main effect of time was significant ($F(3, 46) = 12.912$; $p < .001$), indicating that both training groups increased performance of visual perception to a similar extent.

Trajectory of transfer effects across the training period and their maintenance until follow-up

To trace the source of the effect of the significant group x time interaction for near transfer, we conducted follow-up contrast analyses to compare changes in near transfer

performance between the two training groups across two consecutive measurement points only (baseline vs. intermediate, intermediate vs. post, post vs. follow-up). Results revealed that the effect was driven by a significant group difference in performance change from post to follow-up measurement ($F(1, 48) = 5.709$; $p < .05$; $\eta p^2 = .106$). This effect can be considered medium to large (Cohen, 1988).

Follow-up paired *t*-tests (two-tailed) revealed that only the experimental training group maintained performance in spatial associative episodic memory until four months after training ($t(25) = -1.321$; $p > .05$). The active control training group demonstrated significantly lower scores in the near transfer composite at follow-up compared to post measurement ($t(23) = 2.241$; $p < .05$). Both experimental and active control training groups achieved significant higher scores in the near transfer composite at follow-up compared to baseline (all *p*s < .001). Figure 7 displays mean performance of both training groups in all transfer composites as well as in the visual perception control composite at the four measurement points.

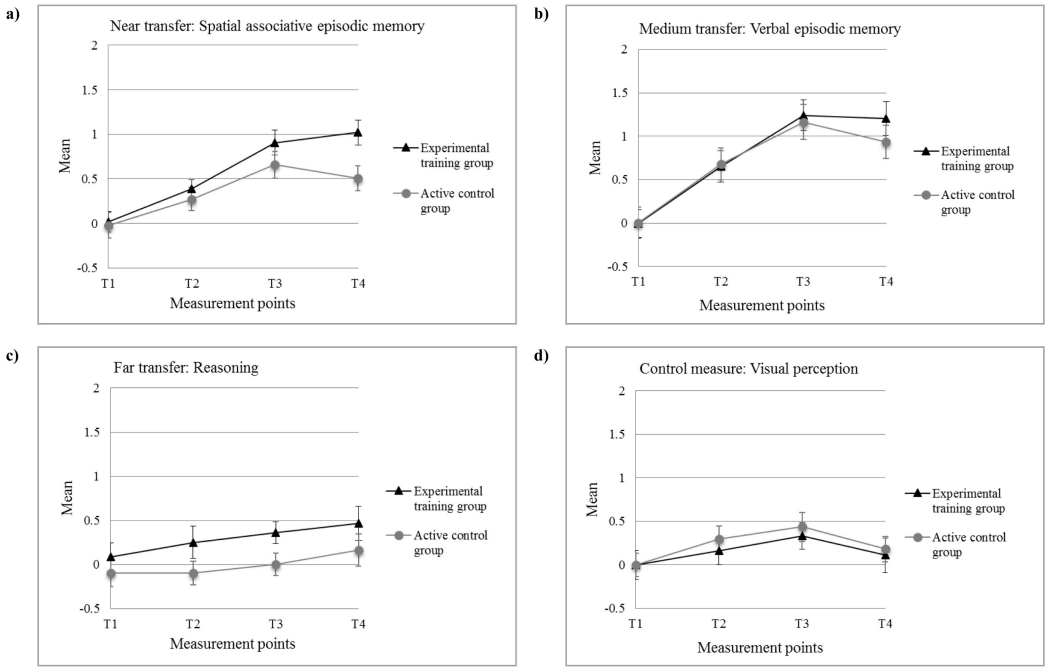

Figure 7. Mean performance of the experimental training group and the active control group in a) the near, b) the medium, c) the far transfer composites, and d) the control measure composite at the four measurement points. Note: The near transfer composite consists of four tasks, the medium transfer composite of two tasks, the far transfer composite of three tasks, and the control measure composite of three tasks. Error bars represent standard errors of the mean.

Association between training gains and transfer effects

For the experimental training group, additional correlation analyses were conducted to assess whether mean training task difficulty level in training sessions 15 and 30 was associated with the near transfer composite at intermediate, post, and follow-up measurement points. Significant medium to large positive correlations (one-sided) were found between mean training task difficulty level in session 15 and near transfer performances at intermediate, post, and follow-up measurements and between mean training task difficulty level in session 30 and near transfer performances at post and follow-up measurements (all rs $> .467$; $p < .01$).

Contribution of individual differences to training effects

To determine who profited most from the training, the experimental training group was divided via median split into 13 low and 14 high training gainers with respect to the mean of the maximally reached difficulty levels in the three training tasks. To test the hypothesis that OLM training participant attributes separate between those who benefit strongly and those who benefit only to a small degree from the investigated training intervention, a discriminant analysis was conducted with age, education, all five assessed personality traits, initial OLM capacity (i.e., mean percentage of correctly recalled object-location associations in the three training tasks in the first training session), initial spatial associative episodic memory ability (near transfer composite), crystallized intelligence, interest, expected success, challenge, and anxiety towards the OLM training as group classification variables. Only four variables, namely the personality trait factor openness to experience, initial spatial associative episodic memory ability, crystallized intelligence, and expected success were significantly different between low and high training gainers and therefore applicable in the discriminant analysis. The Wilks' lambda of .520 indicated a significant discriminant function ($p < .01$) and the

canonical correlation of .693 suggested that the model explained 48.02% of the variation in the grouping variable, i.e., whether a participant was a low training gainer or a high training gainer. Expected training success was the strongest predictor with a standardized canonical discriminant coefficient of .540 for the allocation to low or high training gainers. Initial spatial associative episodic memory ability was next in importance (.481) followed by crystallized intelligence (.422) and openness to experience (.403). The classification results revealed that 81.3% of the originally grouped cases were correctly classified. High training gainers were classified with better accuracy (85.7%) than low training gainers (76.9%).

4.6 Discussion

The current study investigated the efficacy of a six-week process-based OLM training in healthy older adults. Training-induced cognitive changes were assessed using near, medium, and far transfer tasks before, in the middle, and immediately after the training as well as at follow-up four months later. Furthermore, we explored whether individual differences between training participants influenced training gains.

We employed a double-blind design and randomized group allocation. The active control group accounted for potential test-retest influences. Moreover, to rule out effects due to differences in commitment, motivation, and expectation we ensured that both training regimes were identical in terms of structure and procedure (intensity, duration, frequency, stimulus material, feedback). Tasks of the active control training differed from the experimental training only in the targeted cognitive ability and in the lacking performance-adaptive adjustment of training task difficulty. Although one might expect less motivation for this training protocol due to the absence of reinforcement by increases in task difficulty, participants of the control group reported comparable measures of interest in, challenge by, anxiety towards, and expected success in the training as the experimental training group

before and after the completion of the first 15 sessions of the training. Hence, we ensured that the training effects were unlikely the result of psychological phenomena such as expectancy, motivation, and perception effects (Oken et al., 2008).

In addition, we computed composite scores from two to four tasks for each cognitive ability representing near, medium, and far transfer since it has been proposed that improvements in one single task are insufficient to conclude that the underlying ability has also improved (Noack et al. 2009). To this effect, we conducted exploratory factor analyses to confirm that the selected tasks represented the envisaged transfer distance. However, due to similarly high loadings of four tasks on several factors and not enough variability in one other task, we had to exclude a total of five tasks from data analyses.

The experimental training group showed significant linear large performance gains in the OLM training tasks during the six-week training intervention. The magnitude of training gains was significant for all three tasks and similar across both training halfs (session 1 to 15 and session 15 to 30). Regarding generalization to untrained tasks, the experimental training induced near transfer to spatial associative episodic memory. The magnitude of near transfer was of medium effect size. Interestingly, the effect was mainly driven by differences between the experimental and active control group in near transfer performance change from post to follow-up measurement. In fact, near transfer performance of the OLM training group maintained after training termination until follow-up four months later, while active control participants demonstrated significantly lower performance at follow-up compared to post measurement. Regarding medium and far transfer, similar patterns of performance improvements for both training groups were observed. These findings are best attributed to test-retest effects or general positive effects induced by participation in a cognitive training itself. Participants of the active control group demonstrated comparable improvements in the visual perception control tasks as the OLM training participants, indicating that they also

trained visual discrimination.

In the experimental training group, a significant positive association between mean training task difficulty level in sessions 15 and 30 and improvements in near transfer performance assessed immediately and at consecutive measurement points was established, revealing a strong relationship between training gains and near transfer improvements across the study.

The findings in this article are, to our knowledge, the first evidence of near transfer effects induced by a process-based OLM training and their maintenance across four months which may lay the necessary ground for future research on this special type of memory training. Together, the present study documented for the first time the feasibility and efficacy of a process-based OLM training with regard to training gains, transfer, and maintenance.

Although the efficacy of cognitive training is usually evaluated at group level, great inter-individual variability in training effects indicate that some individuals profit more from training than others. While motivational aspects have been discussed to influence the effectiveness of a training, individual differences in age, personality traits, initial level of the to-be-trained cognitive ability, and crystallized intelligence have been reported to be relevant for training outcomes (von Bastian & Oberauer, 2014). In the present study, higher scores in expected training success, initial spatial associative episodic memory ability (near transfer composite), crystallized intelligence, and openness to experience separated high training gainers from low training gainers. Motivation has been strongly linked to self-efficacy, an individual's judgment of his or her capabilities to perform given actions (for reviews see Schunk, 1971; Zimmerman, 2000). It can thus be safely assumed that individuals with great expectations of success – a motivational factor – also experience self-efficacy. Moreover, self-efficacy has been shown to positively relate to memory performance in older adults (e.g., West, Welch, & Thorn, 2001). Compared to low training gainers, high training gainers may

have accomplished higher training gains due to self-perceived capabilities and as a consequence by striving to a greater extent for maximum performance. On the same view, individuals with high initial ability in the same cognitive domain as the to-be-trained tasks may have been able to amplify their resources. Furthermore, crystallized intelligence and openness to experience have been shown to correlate substantially (Ashton, Lee, Vernon, & Jang, 2000). Hence, openness to experience may entail the desire for novel learning situations in combination with an increased need for cognition, a factor which has been reported to positively influence training completion (Jaeggi, Buschkuehl, Shah, & Jonides, 2014). In addition, openness to experience implies less anxiety towards new learning situations. As a result, individuals who are open to new experiences may have had more opportunities to accumulate knowledge and thus display higher crystallized intelligence. Taken together, we view motivation as a key factor contributing to training success. Besides, the way one perceives a learning situation can be influenced. Clearly, motivation associated with self-efficacy has the potential to impact the outcome in learning situations considerably.

So far, findings with respect to the relationship between cognitive performance at baseline and training gains remain controversial. On the one hand, the magnification view suggests that individuals with high initial cognitive ability have the resources available to ameliorate cognitive processes and as a result will gain more from the training intervention than individuals with low initial cognitive ability (e.g., Kliegl, Smith & Baltes, 1990; Lövdén, Brehmer, Li, & Lindenberger, 2012; Verhaeghen & Marcoen, 1996). On the other hand, the compensation view indicates that individuals with high initial cognitive ability are already functioning on an optimal level and as a result have less room for improvement than individuals with low initial cognitive status (e.g., Jaeggi et al., 2008; Karbach & Kray, 2009; Zinke et al., 2011). The former explanation is clearly in accordance with our findings. The fact that in our study participants who profited most from the training not only demonstrated

high initial spatial associative episodic memory performance but also high crystallized intelligence – which is believed to be a result of knowledge and abilities acquired over a lifetime – supports evidence that individuals with high initial capacity in the to-be-trained domain are more likely to increase their abilities to an even greater extent than individuals with low initial capacity. This accumulation of advantages is also referred to as the amplification effect (Lövdén, Brehmer et al., 2012), indicating that participants with a high cognitive status may have a greater potential for cognitive plasticity.

A limitation of our study is the lack of a criterion task. While we have operationalized training gains with respect to maximally achieved training levels over the course of the training, it is unlikely that all individuals exhibited similar initial capacity for the to-be-trained tasks. As a consequence, this could have resulted in the achievement of higher task difficulty levels even if actual training gains were absent. Therefore, in our study, reached difficulty levels as measure for training gains might have been confounded by the individuals' inherent capacities. Thus, training effects would have been better quantified by improved performance of an additional criterion task implemented before and after the training intervention. Ideally, this task would be similar in structure to the experimental training tasks but comprise different stimulus material (e.g., Brehmer et al., 2012; Dahlin et al., 2008). In favor of this view, high training gainers who displayed high spatial associative episodic memory ability (near transfer composite) at baseline may have trained initially under their capacity limits and as a result reached higher difficulty levels than low training gainers. Contrarily, the initial OLM training capacity (mean percentage of correctly recalled object-location associations in the three training tasks in the first training session) did not discriminate between low and high training gainers. Yet, mean training gains correlated significantly with near transfer performance, indicating a strong relationship between training gains and performance of untrained tasks irrespective of initial OLM training capacity.

Therefore, it remains unclear, whether a criterion task would have provided further insights. There are additional caveats worth mentioning. The present study included more women than men, however, this seems to be a known phenomenon in training studies (e.g., Jobe et al., 2001). Moreover, our study sample consisted of young-old adults and participants were highly educated which makes the detection of training effects more likely.

Taken together, we reported in our study the first evidence of immediate and long-term training-induced near transfer effects of a process-based OLM training in older adults. Evidently, this training approach has the potential to ameliorate episodic memory decline in older adults to the extent of transferability to closely related untrained tasks of the same narrow memory ability. In addition, older adults are able to maintain training-induced effects across months. These findings offer a new understanding in terms of theoretical considerations with regard to the efficacy of different training approaches as well as to their practical relevance. While OLM function clearly can be enhanced in old age through extended performance-adaptive practice, the targeted underlying mechanism seems to require a consolidation period – potentially due to the complexity of the processes involved – to fully evolve its potential with respect to transferability. Thus, the present study offers reasons for being optimistic that OLM may possibly be preserved longer in old age through tailor-made interventions that delay or even reverse its decline. It is desirable for prospective studies to pursue a deeper understanding why some individuals benefit more than others from cognitive training interventions. Our findings suggest that motivation as critical baseline variable may contribute considerably to training success in old age. Hence, to draw interest and to raise positive attitudes towards learning situations in older adults will be beneficial to their profits in cognitive training. After all, the comprehensive goal of cognitive training research in old age is to customize future interventions and to make them available to the individuals most in need.

5 NEURAL PLASTICITY INDUCED BY A PROCESS-BASED OBJECT-LOCATION MEMORY TRAINING IN HEALTHY OLDER ADULTS

5.1 Introduction

Objects in our surroundings tend to change their locations frequently, e.g., the places where we store our keys, leave our glasses, or park our cars. Thus, remembering the locations of objects in small- or large-scale surroundings is an integral part of everyday life and relies on the so-called object-location memory (OLM) (Postma et al., 2008).

A distinction needs to be made between OLM acquired from glances from a static viewpoint at the environment and OLM acquired by navigation through the environment. While the former involves a single perspective on our surroundings, the latter relies on the integration of sequentially perceived views of objects and their locations. OLM acquired from static viewpoints is considered to engage declarative memory processes. Conversely, since navigation through the environment usually follows given routes, OLM acquired by navigation can also rely on implicit memory processes such as stimulus-response learning by which the locations of objects are determined by a series of movements at certain landmarks or route junctions (Burgess, 2008; Kessels et al., 2001; Postma et al., 2008). In this article, we refer to OLM as acquired from a static viewpoint which can be operationalized in the context of classical memory models as prototypical type of episodic memory. It involves the intentional encoding of objects *and* their locations in the environment (i.e., their spatial context), the long-term storage as well as the conscious and detailed recollection of these object-location associations.

Generally, key brain areas supporting episodic memory are medial temporal lobe (MTL) regions like the hippocampus and its surrounding structures such as the perirhinal, entorhinal, and parahippocampal cortices as well as the prefrontal cortex (PFC). The

hippocampus is believed to be essential for associative memory processes, that is, for binding different aspects of experienced events into conjoint representations and thereby also for mediating the recollection of contextually rich information. In contrast, the PFC is thought to be engaged in strategic memory processes such as the organization and elaboration of to-be-encoded information, retrieval monitoring, and evaluation of retrieved information (for reviews see Moscovitch et al., 2005; Shing et al., 2010).

Based on their review of previous lesion and functional neuroimaging studies, Postma and colleagues (2004, 2008) proposed a neurocognitive model of OLM. They distinguished between three specific processes involved in OLM: object processing, location processing, and object-to-location binding. The authors suggested that the inferior temporal gyrus supports object processing, while the posterior parietal cortex subserves location processing. Furthermore, the authors proposed that the hippocampus is mainly responsible for binding objects to locations. A recent review of lesion and neuroimaging studies (Zimmermann & Eschen, under review) emphasized in addition to the aforementioned regions the critical roles of supplementary regions in OLM, namely the parahippocampal gyrus for object memory, frontal regions (superior and middle frontal gyrus) for OLM encoding, and occipital regions for additional visual perceptual effort for processing object-location associations compared to processing objects or locations alone. Furthermore, cerebellar regions have been found to be implicated in viewpoint-independent location processing.

Longitudinal studies show that episodic memory declines from 60 years on (Rönnlund et al., 2005; Salthouse, 2010; Schaie, 2005). Both encoding (e.g., Dennis et al., 2008) and retrieval processes (e.g., Morcom, Li, & Rugg, 2007) have found to be less efficient in old age, although retrieval seems to be less affected than encoding (for a review see Friedman, Nessler, & Johnson, 2007). Moreover, compared to young adults, older adults show impairments in both associative and strategic episodic memory processes (Shing et al., 2010).

They demonstrate stronger deficits in episodic memory tasks in which they not only have to retrieve items, but associations of items, of features of items, or of items and their context (Cansino, 2009; for a meta-analysis see Old & Naveh-Benjamin, 2008). Moreover, they show particularly impaired episodic memory performance if it is evaluated by free recall tasks as compared to recognition tasks (Craik & McDowd, 1987), probably because the former tasks pose greater demands on strategic retrieval processes. Congruently, OLM as specific type of episodic memory seems to be vulnerable to aging since it has been repeatedly demonstrated that older adults perform worse than young adults in OLM tasks (for reviews see Kessels & Postma, 2006; Uttl & Graf, 1993).

Episodic memory decline in old age has often been explained by the comparably strong aging-associated deterioration of both gray and white matter integrity of the PFC and the hippocampus, while other mediotemporal areas are affected to a lesser extent (for reviews see Fjell & Waldhovd, 2010; Raz & Rodrigue, 2006; Salthouse, 2011). Empirical evidence also points to age-related structural and functional decline in OLM specific brain regions such as the inferior temporal gyrus and the posterior parietal cortex. They seem to be affected earlier and less strongly than the hippocampus (Raz et al., 2005).

In addition, neuroimaging studies have documented distinct patterns of functional brain activation in older adults in comparison to young adults during episodic memory tasks, that is, reduced brain activity in posterior brain regions as well as in the MTL, but additional activity in the PFC or contralateral brain regions. It is still unclear whether this is a sign of neural inefficiency or neural compensation in the aging brain or of differential strategy use in older as compared to younger adults (for reviews see Dennis & Cabeza, 2008; Maillet & Rajah, 2013; Park & Gutchess, 2005; Park & Reuter-Lorenz, 2009, Zöllig & Eschen, 2009). To our knowledge, age-related differences in OLM specific brain activity have been investigated in three studies so far (Kukolja et al., 2009; Meulenbroek et al., 2010; Schiavetto et al., 2002).

Kukolja and colleagues (2009) examined age differences during OLM encoding and retrieval, whereas the two other studies focused on OLM retrieval. In line with other neuroimaging studies on age differences in brain regions involved in episodic memory, all three studies demonstrated that older participants activated posterior regions specific to OLM (e.g., the left fusiform gyrus, the left hippocampus, the right middle occipital gyrus) to a lesser degree than young adults but additionally frontal regions (e.g., the right anterior cingulate gyrus, left inferior frontal regions) during both encoding and retrieval. Moreover, older adults recruited lateral temporal or striatal brain regions.

In recent years, there is an increasing interest in research on the extent to which aging-associated cognitive decline can be ameliorated through cognitive training. So far, cognitive training targeting episodic memory in healthy older adults has mainly focused on stimulating the recruitment of additional or more efficient cognitive processes for task performance by teaching and practicing explicit memory strategies (e.g., the method of loci, mental imagery). There is convincing evidence for the potential of strategy-based training to enhance episodic memory performance in healthy older adults (for meta-analyses see Gross et al., 2012; Martin et al., 2011; Verhaghen et al., 1992).

In more newly investigated cognitive training interventions, older training participants have been administered repeatedly a set of specific tasks demanding the same cognitive processes. In addition, the difficulty of these training tasks was adapted to the performances of the participants throughout the training period. This so-called process-based training aims at inducing the automation of task-inherent cognitive processes. However, to date, process-based training has mainly targeted executive functions (for reviews see Kueider et al., 2012; Lustig et al., 2009).

While small to medium training gains have been found after strategy-based training compared to passive or active control groups (for meta-analyses see Gross et al., 2012; Martin

et al., 2011; Verhaeghen et al., 1992), medium to large training gains in comparison to passive or active control groups have been reported for process-based training (for reviews and meta-analyses see Hindin & Zelinksi, 2012; Melby-Lervåg & Hulme, 2013; Morrison & Chein, 2011). Importantly, the efficacy of training interventions is not only appraised by the magnitude of performance gains in the trained tasks, but also by the scope of transfer, i.e., by training effects on untrained cognitive abilities. However, up to now, findings remain inconclusive about the faculty of cognitive training to produce transfer effects. This may be caused by great methodological inconsistencies between training studies such as the differential use of control groups (passive or active), training tasks, training procedures, or cognitive outcome measures, and, with regard to the latter, by arbitrary definitions of cognitive transfer distances measured by these outcome tasks (Eschen, 2012; McDaniel & Bugg, 2012; Morrison & Chein, 2011; Noack, Lövdén, & Schmiedek, 2014). With their taxonomy on how to classify the scope of transfer to untrained tasks into near, medium, and far transfer, Noack and colleagues (2009) provided guidelines to categorize transfer distances. So far, strategy-based training has been reported to produce no or seldom transfer to untrained tasks (Lustig et al., 2009; Martin et al., 2011; Verhaeghen et al., 1992), while process-based training has been shown to induce medium to large near transfer effects (Hindin & Zelinksi, 2012; Melby-Lervåg & Hulme, 2013). In addition, the maintenance of training and transfer effects is evaluated by the slope of cognitive functioning from post-training to follow-up assessments months or years after the training. Older adults have been found to maintain training-induced gains in training and transfer task performance up to six years after training completion (Eschen, 2012; Lustig et al., 2009; Zelinski, 2009). However, participants of process-based training have so far been rarely reassessed after training termination.

Up to now, functional brain changes induced by episodic memory training have been demonstrated in few studies. In all these studies, strategy-based episodic memory training was

employed. In some of them, participants had been taught the method of loci, a technique to improve verbal episodic memory by learning to visualize a well-known route of landmarks to which images of the to-be-remembered words are linked during encoding. For retrieval, the landmarks are mentally revisited and the associated words recalled in serial order. In young adults, training-related activity increases were observed in the left fusiform gyrus during both encoding and retrieval as well as in the bilateral prefrontal cortex during encoding and in the left parahippocampal gyrus and the left precuneus during free recall (Kondo et al., 2005). Similar activity increases were demonstrated in young adults in left frontal regions and in young and older participants in left occipito-parietal regions during free recall (Nyberg et al., 2003). These brain regions are known to be involved in mental imagery and thus indicate the recruitment of new cognitive processes demanded by the use of the method of loci. The practice of a semantic encoding strategy (a decision had to be made whether the to-be-memorized words were pleasant or unpleasant as well as personally relevant or irrelevant, then a sentence had to be made which contained each of the to-be-encoded words) led to activity increases mainly in left frontal regions (medial superior frontal gyrus, middle frontal/precentral gyrus, posterior inferior frontal gyrus) and in the left lateral temporal cortex during encoding (Kirchhoff et al., 2012a) as well as in the bilateral hippocampus during recognition (Kirchhoff et al., 2012b) in healthy older adults. Again, the brain regions which showed activity increases were those known to be involved in the newly adopted encoding strategy, that is, semantic processing during encoding and recollection of associated information (sentence) during retrieval.

In contrast, process-based training targeting executive functions in older adults generally leads to training-induced decreases of brain activity in prefrontal and parietal regions with or without accompanying additional recruitment of striatal brain regions compared to active control groups (Brehmer et al., 2011; Dahlin et al., 2008; Erickson et al.,

2007). This may reflect a shift from effortful processing depending on fronto-parietal brain regions to more automatic processing relying on subcortical regions during training.

In conclusion, cognitive training interventions have been found to induce both activity increases and decreases in brain regions associated with the trained cognitive processes. It has been suggested that the adoption of new strategies leads to activity *increases* in brain regions supporting the newly applied additional or more efficient cognitive processes, while the practice of task-inherent cognitive processes stimulates activity *decreases* in brain regions which are specialized for these processes (Eschen, 2012; Kelly & Garavan, 2005).

To our knowledge, only one study investigating cognitive and neural effects induced by an OLM training has been published to date. In the study by Hampstead and colleagues (2012b), cognitively healthy older adults participated in three sessions of a strategy-based OLM training within two weeks and completed a similar OLM outcome task with half trained and half untrained object-location associations (near transfer) before, immediately, and one month after the training. The practiced memory strategy promoted object-location binding. Compared to an active control group who received the same training tasks but was not taught mnemonic strategies, the OLM training participants improved more in the outcome measure from pre- to post-training (medium effect) as well as from pre-training to follow-up (large effect) and showed increased activity in the right hippocampus during cued recall of untrained OLM stimuli from pre- to post-training, that is, in the brain region thought to be predominantly involved in binding of objects to locations.

The course of training-related brain activation changes as a consequence of cognitive training is largely unknown. With regard to temporal trajectories, so far distinct patterns of adaptation have been described for *motor* training, i.e., initial activity in brain regions involved in control processes followed by decreases in these areas due to progressive automation of the practiced task and accompanied by increases in task-relevant motor brain

regions (Kelly & Garavan, 2005). It has been suggested that practice-induced attainment of automated performance is related to *decreased* demands of activity in control and attentional networks such as the PFC, the anterior cingulate cortex (ACC), and the posterior parietal cortex, while *increased* demands – associated with highly practiced performance – are expected in task-specific regions (Kelly & Garavan, 2005). In other words, activation used to cope with novel demands during effortful performance at an early stage of practice/training mainly relates to top-down mechanisms, whereas activation changes due to highly practiced and thus automated task performance tend to be task-specific. So far, functional neuroimaging studies on *cognitive* training effects have mainly implemented pre-post-designs with or without additional follow-up assessments, but mostly ignored the temporal trajectories of training-induced brain activation changes across the training period. By all means, to improve our understanding of how training affects regional brain activity, neural changes need to be monitored at multiple subsequent occasions during the training instead of being assessed only before and after the intervention. First empirical evidence of training-related activation patterns at multiple stages during the training period has been documented by Hempel and colleagues (2004). In particular, they observed in middle-aged participants who received a visuo-spatial working memory training of four weeks initial activity increases in fronto-parietal areas with improved performance after two weeks of training followed by decreases until training termination. This inverse u-shaped function demonstrated that a limited amount of training resulted in an increased recruitment of fronto-parietal regions followed by decreased activity due to more intensive training. However, the interpretation of these results is somewhat ambiguous since the affected brain regions can be viewed as both task-inherent as well as involved in control networks, yet no control group was included in this study. Nevertheless, Kühn and colleagues (2013) provided evidence of a similar activation pattern following working memory training in young adults. Compared to an active control group

who trained on easier tasks of constant difficulty, the experimental training group received an adaptive training which led to initial activity increases in task-inherent brain regions (striatum and putamen) after about one week of daily training followed by decreases in the same regions. In addition, a trend for a similar inverse u-shaped function for fronto-parietal activity was observed for both training groups. While the differences of activation patterns in motor and cognitive training could be related to the way how the tasks were trained (constant difficulty level vs. performance-adaptive progression of difficulty level), it is also important to consider how a particular point in time of the training affects the level of observed brain activity, i.e., which learning stage has been captured.

Hence, to gain a deeper understanding of how an *episodic* memory training alters brain activation, with a special focus on old age, the objectives of the present study were first to identify brain regions affected by a *process-based* OLM training of six weeks in healthy older adults, and second, to examine temporal trajectories of BOLD activation changes across the training period until follow-up. To this end, a group of older adults completed an OLM training of 30 sessions. In contrast, targeting object-location perception, an active control group practiced non-adaptive training tasks. To investigate training-induced changes of brain activation, we used functional magnetic resonance imaging (fMRI) while participants solved an untrained OLM task in the scanner before, in the middle of, and immediately after the training, and four months later. To evaluate cognitive training effects, participants were administered a cognitive test battery assessing near, medium, and far transfer at the same time points.

In the light of the existing findings on brain activation changes induced by process-based training in older adults, we anticipated to observe distinct trajectories of brain activation across the study. Compared to the active control group, we expected for the experimental group activity increases in regions involved in control processes such as the PFC in the first

half of the training during encoding followed by decreases in the second half of the training. We further assumed a similar pattern of initial increases followed by activity decreases in OLM task-inherent brain regions (i.e., inferior temporal gyrus, posterior parietal cortex, hippocampus) during encoding in the second half of the training period. From post to follow-up assessment we hypothesized a general activity increase in these regions. We expected the trajectories to be similar for recognition.

5.2 Methods

Design and procedure

The study was conducted as a randomized controlled double-blind trial with a two-group design, i.e., an experimental training group (OLM group) receiving a performance-adaptive OLM training and an active control group (CON group) who was administered a non-adaptive object-location perception (OLP) training. Methods are described in more detail elsewhere (Zimmermann, Martin, Röcke, & Eschen, in preparation).

Training was accessible from the participants' homes via the open-source software Tatool (von Bastian et al., 2013). They included 30 sessions, divided into two training blocks of 15 sessions within three weeks each, with a break of one week in between. Participants could not train more than once a day. Before the first training session, participants took part in a training introductory session of 60 min. Both groups trained three different tasks which were presented in randomized, but counterbalanced order across participants.

Prior to inclusion in the study, prospective study participants filled out a screening questionnaire at home and took part in a 1.5 h screening session. Those meeting the inclusion criteria participated in a cognitive and a neuroimaging outcome session conducted within a week at following four measurement points: a baseline measurement before the training (T1), an intermediate measurement in the middle of the training (T2), a post measurement after

training completion (T3), and a follow-up measurement four months later (T4). Cognitive outcome sessions lasted 2.5 h with two 15-min breaks. During these sessions, one to four participants completed several cognitive tests assessing near (spatial episodic memory), medium (verbal episodic memory) as well as far transfer (reasoning), and, as a control measure, visual perception. The duration of the neuroimaging sessions was 1.5 h. They were conducted individually. Functional MRI, structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), and fluid-attenuated inversion recovery (FLAIR) measurements were acquired. During fMRI sessions, participants completed a non-trained OLM task. In this article, we report results of the cognitive transfer and fMRI assessments. See Figure 8 for an overview of the study design.

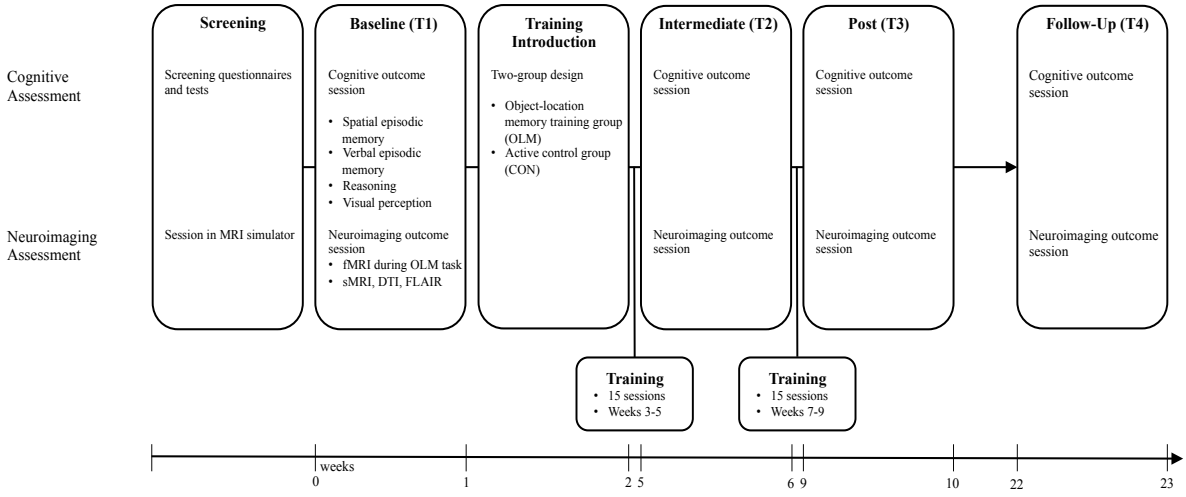

Figure 8. Study design and timeline.

Participants

Participants were recruited at lectures for senior citizens at the University of Zurich, through newspaper articles, advertisements in magazines, public talks, flyers, and word of mouth. Inclusion criteria for study participation were age between 60–75 years, right-handedness, native German speaker or fluent in German, basic computer and internet experience, and access to a computer and the internet during the training period. Exclusion

criteria were history of previous or current neurological and psychiatric disorders or substance use negatively affecting brain function, sensory and motor deficiencies hindering completion of training and outcome measurements, violation of MRI safety requirements, and participation in a training study within the last five years. If inclusion criteria were met, potential participants were individually tested in a screening session at the International Normal Aging and Plasticity Imaging Center (INAPIC) for cognitive deficits indicative of Mild Cognitive Impairment (MCI) or dementia with the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-NAB; Berres et al., 2000) which includes the Mini Mental State Examination (MMSE; Folstein et al., 1975) and for clinical depression with the short version of the Geriatric Depression Scale (GDS; Sheik & Yesavage, 1986). Participants also completed a crystallized intelligence test (Spot-a-Word: MWT-B; Lehrl, 1977). Furthermore, to reduce anxiety and for practicing the fMRI paradigm, they took part in a short training session in an MRI simulator. Participants who scored 1.5 *SD* below age-, gender-, and education-specific norms in more than one subtest of the CERAD-NAB, had a sum score > 5 in the short version of the Geriatric Depression Scale, or had an incidental finding detected at the first neuroimaging session were excluded from study participation.

The study was approved by the Ethics Committee of the Canton of Zurich. All participants gave written informed consent. They received 320 CHF (approx. 340 USD) for their participation in the study. Details of the recruitment process and reasons for excluding participants from study participation can be seen in Figure 9. Six individuals had to be excluded due to failed screening tests, incidental findings, or claustrophobia. Two participants dropped out during the study. Moreover, four participants were excluded from statistical analyses due to more than a total of 5% movement artifacts in the experimental conditions of fMRI acquisition and one participant who could not attend follow-up assessments for medical

reasons. A total of 46 participants were included in the final statistical analyses (28 women, 18 men; M_{age} = 67.00, *SD* = 3.85, age range 60–75 years), i.e., 24 participants of the experimental OLM training group and 22 participants of the CON group who completed the object perception training (OLP).

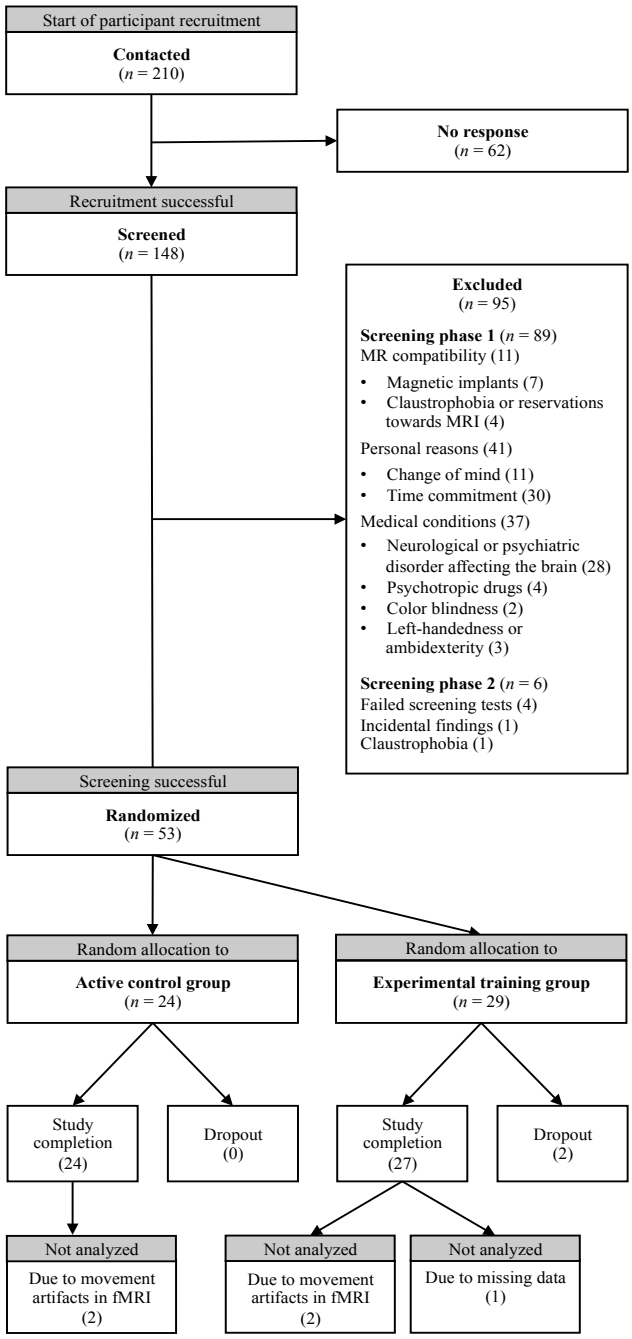

Figure 9. Recruitment process and reasons for excluding participants from study participation and statistical analyses.

Training

OLM training (experimental training)

In each training session, a shape-location task, a landmark-location task, and an object-location task with 10 trials each had to be completed. All tasks allowed individualized performance-adaptive progression of difficulty level. The latter was defined by the number of to-be-encoded object-location associations and increased by one association from one difficulty level to the next higher. Each task of each new training session started at the difficulty level on which the participant ended in the previous session or one difficulty level higher or lower. If performance accuracy was above 70% in a training task in one training session, the next higher difficulty level in this training task in the next training session had to be completed. If a performance accuracy between 50–70% in a training task in one training session was reached, the difficulty level remained the same in this task in the next training session, and if performance accuracy was below 50%, participants trained on a lower difficulty level in this training task in the next training session. The lowest difficulty level comprised two stimuli and was given in the first session. Twenty difficulty levels for each task were prepared. Each training task trial consisted of an encoding, a distractor, and a retrieval phase. During the encoding phase of the shape-location task and the landmark-location task, 2–21 stimuli (shapes or buildings, respectively) were presented simultaneously for 6–63 s in a 6x6-grid. For the landmark-location task, the grid was superimposed by a different fictitious city map in each training session. For the object-location task, 2–21 objects were presented serially in a 5x6-grid for 4 s each with an interstimulus interval (ISI) of 0.5 s. Locations of stimuli were randomly allocated across the 10 trials of the training tasks in each session. Stimuli were supplied from databases of 261 geometrical shapes (29 different shapes in nine colours), 261 photographs of buildings drawn from several websites (see supplementary material), or consisted of 245 pictures of everyday objects (Rossion &

Pourtois, 2004; Snodgrass & Vanderwart, 1980). Within a training session, different stimuli were presented in each training task trial.

The encoding phases were followed by subsequent distractor phases, each lasting for 20 s. For the shape-location task, 10 words had to be clicked on in alphabetical order, for the landmark-location task, 10 two-digit numbers had to be clicked on in order of their magnitude, and for the object-location task, serially presented simple arithmetic calculations had to be evaluated with respect to their accuracy. After each distractor trial, participants received performance feedback.

During the retrieval phases of the shape-location and the landmark-location task, previously presented empty grids or maps were displayed with the encoded 2–21 objects on the left side, and participants had to relocate them to their encoded locations by mouse click (duration 12–126 s). The retrieval phase of the object-location task consisted of 2–21 serially presented objects which had to be relocated to their encoded locations one at a time. Each object was presented for a maximum of 6 s. After each mouse click or after 6 s, the next object was presented for relocation (duration 12–126 s).

At the end of each retrieval trial, training task, and training session, participants received feedback about the current difficulty level as well as about the percentage of the correctly relocated objects per trial or across the 10 trials of each training task, respectively.

OLP training (active control training)

The trials of each of the three OLP tasks were divided into a first perception phase, a distractor phase (same as in the matching OLM training task), and a second perception phase. Each OLP training participant was randomly matched to one of the OLM training participants who had started the training at least one week before. The durations of the two perception phases were determined by the durations of the encoding and retrieval phases of the

corresponding training task in the same training session of the individually matched OLM participant.

For the two perception phases of the shape perception task, a 6x6-grid was presented filled with 36 different shapes which were randomly drawn from the shape database of the shape-location experimental training task. Above the grid, a target shape was displayed which participants had to find as quickly as possible within the grid and indicate by mouse click. Subsequently, a new grid was shown. The two phases of the landmark perception task were identical to the shape perception task but comprised a fictitious map superimposed on the 6x6-grid which contained 21 photographs of buildings. Again, a target stimulus was presented above the map and had to be found within the map as quickly as possible and indicated by mouse click. The building stimuli were drawn from the building database of the landmark-location experimental training task. In the two perception phases of the object-perception task, participants were presented two 1x10-grids filled with objects, one above the other. The bottom grid differed from the upper grid in one of the 10 object drawings. Participants had to indicate this target object as quickly as possible by mouse click. Object stimuli were drawn from the object database of the object-location experimental training task.

Performance feedback was given after each mouse click during the two perception and distractor phases, at the end of each perception phase, each training task, and each training session and included performance accuracy and reaction time.

Cognitive transfer assessments

All participants completed an extensive cognitive test battery at all four measurement points measuring near, medium, and far transfer, and, as a control measure, visual perception. Transfer distances were determined on theoretical grounds (Noack et al., 2009). Near transfer was assessed with the three paper-and-pencil tasks measuring spatial episodic memory from

the Berlin Intelligence Structure Test Form (BIS-4; Jäger et al., 1997), i.e., the Remembering Route Task, the Orientation Memory Task, and the Company Sign Task. In addition, a computerized OLM Pairs Task adapted from Rasch and colleagues (2007) was administered. Furthermore, the task which participants solved while in the scanner (In-scanner OLM task) served as fifth near transfer task (see below). Medium transfer was measured with the three verbal episodic memory tasks from the BIS-4, i.e., the Meaningful Text Task, the Remembering Words Task, and the Fantasy Language Task. Finally, far transfer comprised six tasks measuring reasoning, i.e., the five spatial reasoning tasks from the BIS-4 (Analogies Task, Charkov Task, Bongard Task, Shape Selection Task, Transaction Task), and the short form of the Raven's Advanced Progressive Matrices Test (Arthur & Day, 1994). To examine the control measure visual perception, the three paper-and-pencil tasks representing the cognitive factor visual perceptual speed from the Kit of Factor-Referenced Cognitive Tests (Ekstrom et al., 1976) were conducted, i.e., the Finding A's Test, the Number Comparison Test, and the Identical Pictures Test.

In-scanner OLM task

In scanner, participants performed an untrained OLM task. A block design was used, consisting of 24 blocks that were equally divided between two runs. Each run lasted approximately 14 min. The order of the two runs was counterbalanced across participants of both the OLM and the CON groups. Before entering the scanner, participants completed five practice trials of the task on a laptop.

In the MR scanner, participants lay comfortably in supine position with padded head holders restricting head movements. Stimuli were presented using the software Presentation (NeuroBehavioral Systems; NBS) which also recorded behavioral performance. The stimuli were presented on MR compatible goggles (Resonance Technology Inc., Northridge, USA)

which could be adjusted for poor eyesight. Object stimuli were drawn from the Bank of Standardized Stimuli (BOSS) created by Brodeur and colleagues (2010). For the present study, the 480 colored everyday objects were divided into two sets with comparable familiarity and object identity ratings (provided by Brodeur, Dionne-Dostie, Montreuil, & Lepage, 2010). After eliminating photo stimuli which were semantically very similar (i.e., wire, cable) and stimuli that were mostly white in color because of the white screen background, 144 stimuli for each fMRI run remained. The same number of similarly rated stimuli was used for each encoding phase. Stimuli were used only once within both runs. They were different from the object stimuli used for the OLM and OLP training tasks.

A block of the In-scanner OLM task included four phases: encoding, distractor, recognition, and visual fixation baseline. Stimuli were presented in a 5x5-grid on a white background. During the encoding phase, six objects were presented serially in one of the grid cells, each for 3000 ms (ISI = 0 ms). During the distractor phase, participants were asked to solve a 1-back task. Black arrows were presented consecutively in random order and participants had to decide whether the presented arrow pointed towards the same direction as the previous one and to indicate their decisions by pressing two buttons of an MR compatible response box with their left or right thumbs (same direction = left, different direction = right). Each cue lasted for 1000 ms followed by an ISI of 1000 ms. The distractor phase was randomly jittered and lasted for 12000 to 18000 ms. During the recognition phase, participants were presented the six encoded objects subsequently in the 5x5-grid, each for 3000 ms (ISI = 0 ms). Three of the objects appeared in the same locations as during encoding, whereas three objects were presented in locations in which different objects had been displayed during encoding. Participants had to decide whether presented object-location associations were the encoded ones or not and indicate their decisions by pressing two buttons of the response box with their left or right thumbs. The following visual fixation baseline

phase was jittered and lasted between 9000 to 15000 ms. During this period, a black cross was presented that changed to green 2000 ms before the encoding phase of the next block started. The In-scanner OLM task is displayed in Figure 10.

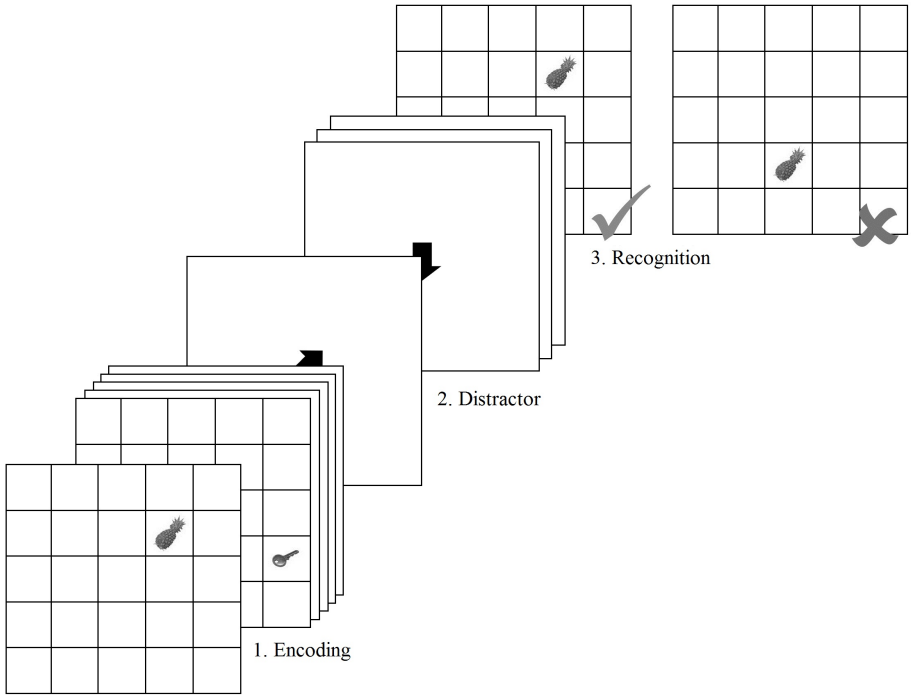

Figure 10. In-scanner OLM task.

MRI protocol

Whole brain T2-weighted EPI-BOLD data were acquired with a Philips Achieva 3T TX scanner (Philips Medical Systems, Best, the Netherlands) using a 32-channel receiver head coil array. Blood-oxygen-level-dependent (BOLD) fMRI images were generated with a gradient-echo-planar-imaging (EPI) pulse sequence (TR/TE = 2500/30 ms, flip angle = 84°, matrix = 80x80, FOV = 24x24 cm, 44 slices, slice thickness 3 mm, 0.5 mm interslice spacing), that yielded 3x3x3 mm^3 voxels. Slices were acquired in descending order and in transverse orientation. Each of the two runs consisted of a total of 335 volumes. Five dummy scans were performed prior to image acquisition aiming to eliminate signals arising from progressive saturation. To reduce undesired noise of physiological processes during fMRI time series, cardiac and respiratory functions were monitored using a pneumatic belt placed

around the participants' abdomen and by recording the electrical activity of their hearts (ECG), respectively. In addition, a high-resolution T1 anatomic image (TR/TE = 8.1/3.7 ms, flip angle = 8°, matrix 240x240, FOV = 24x24 cm, 160 slices, slice thickness 1.0 mm, 1x1x1 mm^3 voxels) was obtained for each subject.

Data analyses

Image processing and fMRI data analysis

Functional images were analyzed with the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2013b. For preprocessing, individual structural images were co-registered to the structural T1 template implemented in SPM8 followed by segmentation into gray matter, white matter, and cerebrospinal fluid (CSF). Individual T1 images were bias-corrected with respect to the intensity of the image with SPM8. The EPI images of each time series were then synchronized to the middle slice to account for differences in slice acquisition time and spatially realigned to the mean image to correct for head movement artifacts between scans. Individual functional mean images were co-registered to the bias-corrected individual structural T1 images and then normalized to the standard stereotactic space (MNI152; avg. T1 template provided by the Montreal Neurological Institute) using a 12-parameter-affine transformation. Afterwards, functional data were smoothed with a Gaussian kernel of 8 mm full-width-at-half-maximum (FWHM). The data were high-pass filtered with a cut-off of 128 s to remove subject-specific low-frequency drifts in signal changes.

In addition, we utilized the Artifact Detection Tools (ART) (http://www.nitrc.org/projects/artifact_detect/) to ensure that scans with large motion artifacts were not included in the statistical analysis. Parameters were set at a global *z*-threshold of 9 and a motion threshold of 2 mm. Outliers were thus defined by the global mean image

intensity differing by more than 9 standard deviations (*z*-threshold) from the mean of the entire series of time frames per scan and by motion displacement of more than 2 mm to the previous time frame. Outliers were introduced by individual regressors into the individual first-level models.

Using the PhysIO Toolbox (http://www.translationalneuromodeling.org/tnu-checkphysretroicor-toolbox/), we performed a physiological noise correction (Glover, Li, & Ress, 2000) by using Fourier expansions of different order for the estimated phases of cardiac pulsation, respiration, and cardio-respiratory interactions *(*Harvey et al., 2008). The corresponding individual physiological confound regressors were computed using MATLAB (Hutton et al., 2011) and entered into the individual first-level models.

Statistical analyses were performed using the general linear model approach (GLM) as implemented in SPM8. Explanatory variables modeling the experimental conditions of the blocked fMRI design comprised the following four conditions: (1) encoding, (2) distractor, (3) recognition, and (4) visual fixation baseline.

In the first-level analysis, these four conditions were modeled for each fMRI session (each consisting of two runs), separately for T1, T2, T3, and T4. Furthermore, the model included the six individual movement regressors from the realignment process and additionally the individual regressors for deleted movement outlier scans (ART) and physiological noise (PhysIO). The following phases were of special interest: (1) encoding vs. visual fixation baseline and (2) recognition vs. visual fixation baseline. To this effect, the visual fixation phase trials were introduced as implicit baseline into the model. The coefficients for each contrast were then estimated separately in fixed effect models.

For the second-level analysis, individual contrasts of interest (encoding vs. implicit baseline and recognition vs. implicit baseline) were used to estimate training-related modulation of brain activation across time. The distractor phase was introduced into the

model as regressor of no interest. Aiming for population-level inferences, we used individual contrasts for encoding and recognition in the following whole brain random effect analyses: To identify brain regions affected by the OLM training during encoding vs. implicit baseline and recognition vs. implicit baseline – independent of In-scanner OLM task performance – we conducted a flexible factorial model in SPM8 with group (OLM, CON) as between-subject factor and time (T1, T2, T3, T4) as within-subject factor and with In-scanner OLM task performance as covariate of no interest. Variance was assumed to be unequal for the factor group and equal for the factors subject and time. We were particularly interested in the main effect of time and the interaction group x time [$p < .001$ (unc.), k = 30]. The resulting cluster locations were labeled using the Harvard-Oxford cortical/subcortical structural atlas and the Juelich Histological atlas provided by FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). For anatomical reference, functional images were registered to high-resolution structural images on a MNI152 standard brain. Images are displayed in neurological convention.

5.3 Results

Behavioral data

Comparison of experimental groups for demographics and screening variables

Behavioral analyses were conducted with SPSS20 (http://www.spss.com) and MATLAB R2013b (Mathworks Inc., MA, USA).

A multivariate analysis of variance (MANOVA) with group (OLM, CON) as between-subject factor and demographic characteristics (besides gender) and screening measures as dependent variables demonstrated no significant differences in these variables between the two experimental groups ($F(7, 38) = 0.683$; $p > .05$). The gender distribution did also not significantly differ between the OLM and CON groups ($\chi^2(1) = 0.056$; $p > .05$). Table 5 displays demographic characteristics of the study participants.

Table 5. Demographic characteristics of the final study participants at baseline

	Experimental training group (*n* = 24) *M* (*SD*); range	**Active control training group (*n* = 22)** *M* (*SD*); range	**Total (*N* = 46)** *M* (*SD*); range
Age	66.54 (3.81); 60–75	67.50 (3.92); 61–75	67.00 (3.85); 60–75
Gender (male: *n* (%) / female: *n* (%))	9 (37.5%) / 15 (62.5%)	9 (40.9%) / 13 (59.1%)	18 (39.1%) / 28 (60.9%)
Education in years	15.42 (3.69); 9–24	14.14 (3.17); 10–20	14.80 (3.47); 9–24
Computer experience in years	18.09 (8.75); 2–45	18.14 (7.46); 4–32	18.11 (8.07); 2–45
Internet experience in years	12.24 (6.61); 0.83–25	11.77 (5.73); 4–25	12.01 (6.14); 0.83–25

OLM training

To analyze the trajectory of mean training task difficulty levels across the 30 training sessions, polynomial contrasts for time were used. Results revealed a significant positive linear trend (large effect) indicating that mean training performance increased linearly across all training sessions ($F(1,23) = 55.76$; $p < .001$; $\eta p^2 = .708$). Figure 11 displays the mean training task difficulty levels across the 30 training sessions.

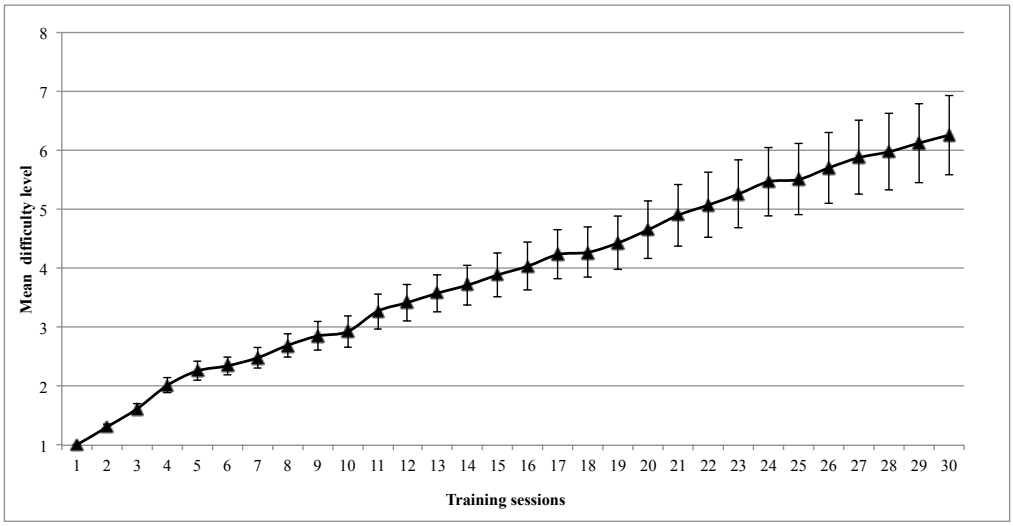

Figure 11. Mean training task performance gains of the OLM group. Error bars represent standard errors of the mean.

Cognitive transfer assessments

We identified outliers in our transfer data by the median absolute deviation (MAD) and replaced them with the median of the raw scores plus or minus three times the MAD (for calculation of MAD, see Leys et al., 2013). Composites for near, medium, and far transfer as well as for the visual perception control measure were computed by first *z*-standardizing the raw data of all cognitive outcome tests with respect to the means and standard deviations of the whole sample at baseline measurement. One task was excluded due to very little variability across time. Following explorative factor analysis (principal component analysis with orthogonal rotation), four further tasks were removed from analyses due to similarly high loadings on several factors.

A 2x4 MANOVA with group as between-subject factor (OLM, CON) and the four cognitive composites as dependent variables revealed that the two training groups did not differ at baseline with respect to cognitive transfer and control measures ($F(4, 41) = 0.307$; $p > .05$). For the detection of possible transfer effects, we used a mixed 2x4 MANOVA with group (OLM, CON) as between-subject factor and time (T1, T2, T3, T4) as within-subject factor with the three transfer composites as dependent variables. The main effect of time was significant ($F(9, 396) = 14.955$; $p < .001$; $\eta p^2 = .254$) indicating an increasing performance in all transfer composites for both groups across time, however, the main effect of group was not significant ($F(3, 42) = 1.055$; $p > .05$). The group x time interaction approached significance ($F(9, 396) = 1.750$; $p = .076$). Follow-up mixed 2x4 analyses of variance (ANOVA's) were conducted separately for each transfer composite. For spatial episodic memory (near transfer), there was a significant large main effect of time ($F(3, 42) = 39.549$; $p < .001$; $\eta p^2 = .739$), no main effect of group ($F(1, 44) = 1.890$ $p > .05$), and a significant group x time interaction ($F(3, 42) = 3.843$; $p < .05$; $\eta p^2 = .215$; large effect). For medium and far transfer composites, significant main effects of time were observed (all ps $< .05$), but no significant main effects of group nor significant group x time interactions. To test how the experimental and the active control training regimes affected performance in the visual perception control composite across time, we computed a 2x4 mixed ANOVA with group (OLM, CON) as between-subject factor and time (T1, T2, T3, T4) as within-subject factor. Results indicated a significant main effect of time ($F(3, 132) = 12.904$; $p < .001$; $\eta p^2 = .227$; large effect), no significant main effect of group ($F(1, 44) = 0.382$; $p > .05$), and no significant group x time interaction ($F(3, 132) = 0.282$; $p > .05$). Further analyses revealed (for more details see Zimmermann, Martin, Röcke, & Eschen, in preparation), that both training groups increased their performance in verbal episodic memory, reasoning, and visual perception to a similar degree during the training period (measurement points T1–T3) and maintained their performance gains

comparably from post-training until follow-up. In contrast, the OLM group showed greater spatial episodic memory performance gains than the CON group across the whole study period, that is, OLM training participants improved in spatial episodic memory to a greater degree from pre-training to follow-up, whereas OLP training participants showed a slightly lower spatial episodic memory performance at follow-up compared to post-training.

In-scanner OLM task

At baseline, performance accuracy was above chance level for both training groups (OLM: M = 79.95%, SD = 6.42; CON: M = 80.24%, SD = 8.27), but was not significantly different ($t(44) = 0.135$; $p > .05$). To assess performance increases across the four measurement points, we computed a 2x4 mixed ANOVA with group as between-subject factor (OLM, CON) and time as within-subject factor (T1, T, T3, T4). Results indicated a significant large main effect of time ($F(3, 42) = 21.303$; $p < .001$; $\eta p^2 = .603$), no significant main effect of group ($F(1, 44) = 0.876$; $p > .05$), and most importantly, a significant interaction group x time ($F(3, 42) = 3.051$; $p < .05$; $\eta p^2 = .179$). According to Cohen (1988), the interaction effect is large.

To trace the source of the effect, we conducted follow-up contrast analyses to compare changes between the two groups and two consecutive measurement points only. Results revealed only a significant large main effect of time for T1 vs. T2 ($F(1, 44) = 18.336$; $p < .05$; $\eta p^2 = .294$), a trend towards significance for T3 vs. T4 ($F(1, 44) = 2.962$; $p = 0.92$), no main effect of group and no significant group x time interactions for consecutive measurement points (all ps > .05).

Figure 12 displays the performance changes of both training groups in the In-scanner OLM task across the four measurement points.

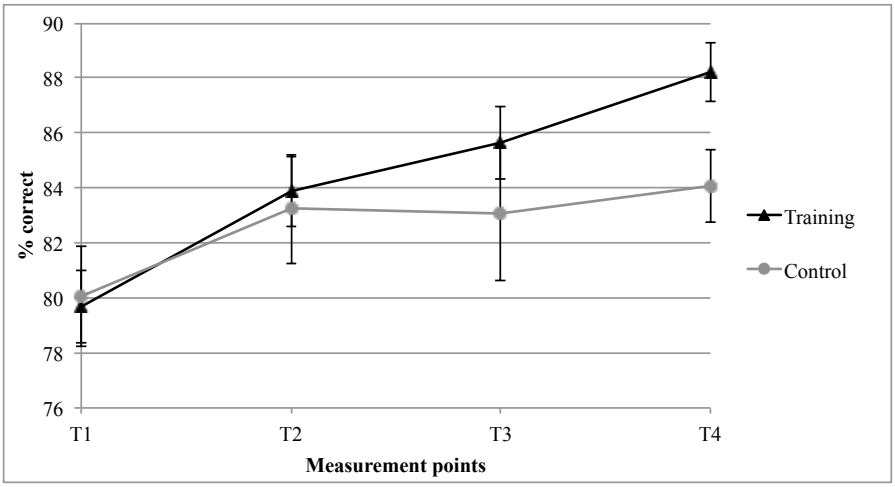

Figure 12. Trajectories of In-scanner OLM task performance (% correct) of the OLM group and the CON group across time. Error bars represent standard errors of the mean.

fMRI data

Main effect of time on brain regions involved in In-scanner OLM task encoding and recognition

We explored how time affected brain activation during the encoding and recognition phases of the In-scanner OLM task in both groups independent of performance accuracy. During encoding, activity increases between T1 and T3 followed by decreases between T3 and T4 were observed in occipito-parietal regions. Continuous decreases were found mainly in frontal regions. For recognition, only activity increases between T1 and T3 followed by decreases from T3 to T4 were evident in occipital brain regions and one middle frontal region. Table 6 displays brain regions with changing activity across study time.

Table 6. Main effect of time on brain changes across study

Brain area		# voxel	BA	x	y	z	*Z* max	*F*
Encoding								
Increases from T1 to T3 followed by a decrease between T3 and T4								
Occipital pole	L	337	18	-22	-94	12	4.53	10.56
	R	313	18	30	-92	12	4.46	10.26
Superior parietal lobule	L	527	7	-16	-70	56	4.44	10.17
	R	302	7	14	-72	54	4.20	9.12
Inferior parietal lobule	R	31	39	42	-80	24	3.88	8.14
Decreases from T1 to T4								
Inferior parietal lobule	L	292	39	-46	-60	32	4.57	10.69
Superior frontal gyrus	L	735	8	-8	32	60	4.45	10.22
Middle frontal gyrus	L	48	9	-38	12	48	4.06	8.77
Frontal pole	L	95	9	-22	50	28	3.29	6.30
Recognition								
Increases from T1 to T3 followed by a decrease between T3 and T4								
Precuneus	R	2041	-	4	-58	50	5.24	13.70
Occipital pole	L	146	18	-18	-94	8	3.95	8.37
Middle frontal gyrus	R	42	48	40	20	28	3.89	8.16
Fusiform gyrus	R	536	18	24	-84	-10	3.45	6.75

Note. *F*-effects are listed at $p < .001$, uncorrected, k = 30. Coordinates x, y, z are reported in MNI space.

Brain regions differentially affected by the OLM training and temporal trajectories of their changes

Interaction analyses (*F*-contrasts) with group (OLM, CON) as between-subject factor and time (T1, T2, T3, T4) as within-subject factor revealed significant differential brain activation trajectories for the two groups across the study period only for the contrast encoding vs. implicit baseline. Results indicated different brain activation trajectories across the study period in both groups in frontal regions (bilateral anterior cingulate cortex (ACC), right posterior cingulate cortex (PCC), and left insular cortex). Furthermore, separate group x time interaction analyses for two consecutive measurements points yielded significant group differences in brain activation trajectories between T1 and T2 in the left ACC and between T2 and T3 in the right hippocampus and left temporal pole. Finally, the two groups did not differ in brain activation trajectories between T3 and T4. Table 7 displays brain regions which were differentially affected by the OLM training in comparison to the OLP training across time in more detail.

During encoding, continuous decreases in brain activity from T1 to T3 followed by a slight increase at T4 were observed in the OLM group in the left ACC and left insula, while brain activity increased between T1 to T3 in the CON group followed by a decrease between T3 and T4 (Figure 13A and C). For the right ACC, continuous decreases in brain activity from T1 to T4 were found in the OLM group and continuous increases in brain activity from T1 to T4 in the CON group (Figure 13B). Furthermore, in the right PCC, an initial activity increase between T1 and T2 was succeeded by a decrease between T2 and T4 in the OLM group. For the CON group, a decrease in brain activity was observed between T1 and T2 followed by an increase between T2 and T3 and a decrease between T3 and T4 (Figure 13D).

Table 7. Brain regions differentially affected by OLM in comparison to OLP training across time during In-Scanner OLM task encoding

Brain area		**# voxel**	**BA**	**x**	**y**	**z**	***Z* max**	***F***
2x4 interaction group (OLM, CON) x time (T1, T2, T3, T4)								
Anterior cingulate	L	288	24	-4	38	10	4.82	11.74
Anterior cingulate	R	288	32	8	42	14	4.46	10.26
Insula	L	66	48	-36	2	-8	3.70	7.54
Posterior cingulate	R	31	27	14	-42	4	3.62	7.20
2x2 interaction group (OLM, CON) x time (T1,T2)								
Anterior cingulate	L	50	24	-4	38	10	4.10	19.49
2x2 interaction group (OLM, CON) x time (T2, T3)								
Hippocampus	R	44	27	16	-40	4	3.50	14.35
Temporal pole	L	37	38	-48	14	-18	3.36	13.26
2x2 interaction group (OLM, CON) x time (T3, T4)								
-								

Note. *F*-interaction effects are listed at $p < .001$, uncorrected, k = 30. Coordinates x, y, z are reported in MNI space.

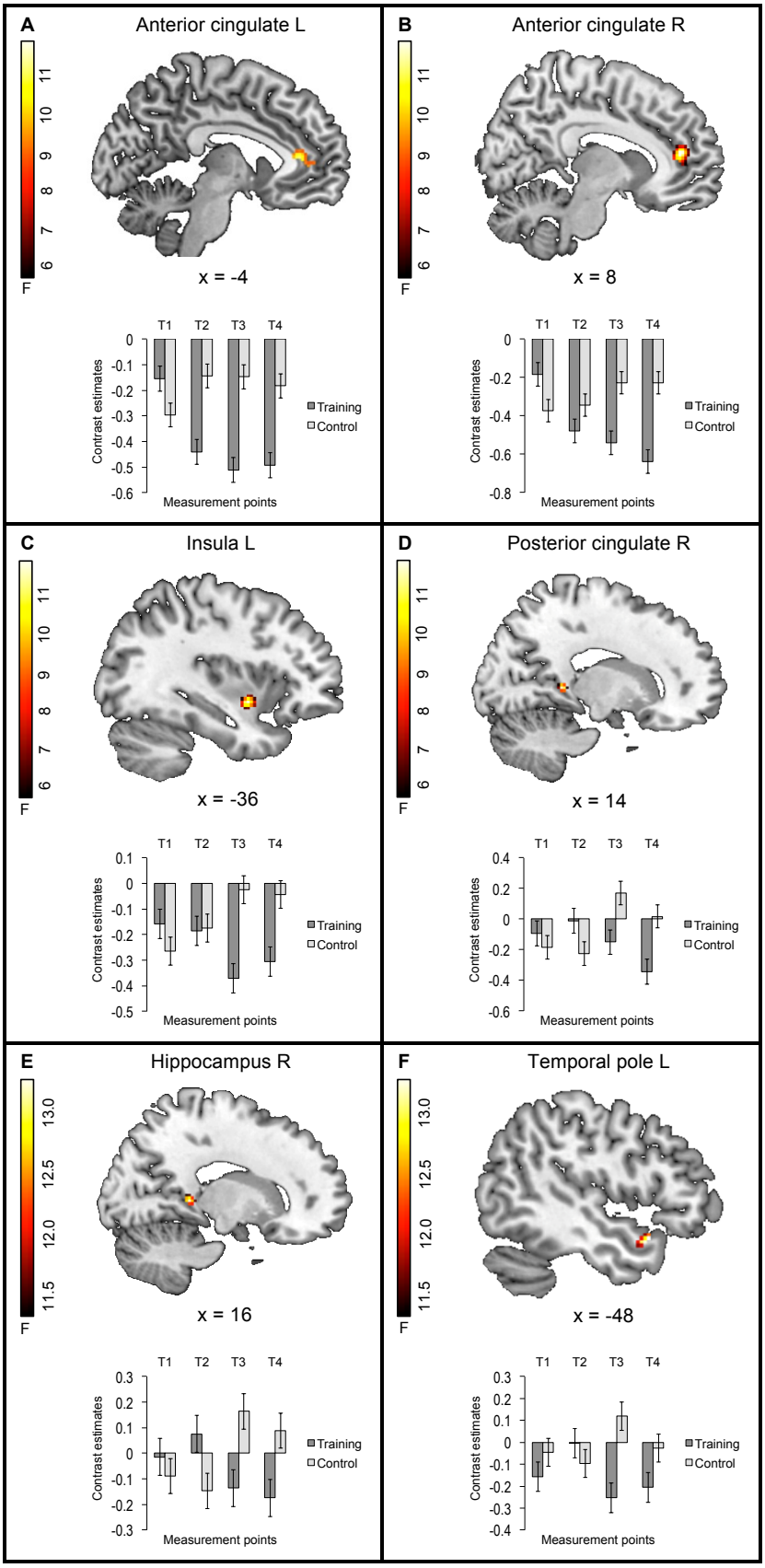

Figure 13. Trajectories of brain activation during In-scanner OLM task encoding of both OLM and CON groups in brain regions differentially affected by OLM vs. OLP training. Figures A–D refer to group x time interactions of T1, T2, T3, and T4. Figures E and F refer to group x time interactions of T2 and T3. Error bars represent standard errors of the mean.

In addition, reduction of brain activity in the right hippocampus and the left temporal pole from T2 to T3 was found in participants of the OLM group, while for the CON group activity increases across these two measurement points were observed (Figure 13E and F). Across all four measurement points, an increase in brain activity was detected in the right hippocampus between T1 and T2 in the OLM group followed by a continuous decrease from T2 to T4. In the CON group, an activity increase was found between T2 and T3. Between all other measurement points, only decreases were observed. Similar brain activation trajectories were seen for both training groups in the left temporal pole across the training period.

5.4 Discussion

The aims of the current study were to identify brain regions affected by a *process-based* OLM training of six weeks in healthy older adults and to examine temporal trajectories of BOLD activation changes across the training period until follow-up. For that reason, a group of 24 older adults receiving a performance-adaptive process-based OLM training was compared to a group of 22 older adults who were administered a non-adaptive OLP training. To examine brain regions differentially affected by the OLM training as well as their activation changes during the training period and until four months later, we assessed brain activity while participants solved an untrained OLM task in the scanner before, in the middle of, and immediately after the training as well as four months later. Furthermore, all participants completed a cognitive test battery assessing near, medium, and far transfer.

Six weeks of OLM training resulted in significant training gains. Moreover, training task performance increased linearly across all 30 training sessions. An indication of near transfer was observed, i.e., compared to the CON group, the OLM group demonstrated increasing performance in tasks assessing spatial episodic memory across time. However, neither medium nor far transfer effects were found. Participants of both OLM and CON

groups demonstrated similar performance increases in visual perception control measures. In addition, the OLM group showed significantly larger improvements in the In-scanner OLM task across time compared to the CON group.

Main effect of time on brain regions involved in the In-scanner OLM task

Across the study, similar activation changes across the four measurement points were observed in both training groups in several brain regions. Independent of In-scanner OLM task performance, increased activity during the training period with a slight decrease at follow-up was observed in brain regions relevant for the perception of visuo-spatial stimuli, i.e., in occipito-parietal regions during encoding (bilateral superior parietal lobule, right inferior parietal lobule, bilateral occipital pole) and during recognition (right precuneus, right fusiform gyrus, left occipital pole). We interpret the increased activity in brain regions involved in the perception of the stimuli material used in both OLM and OLP training regimes as a result of increased practice-related performance. Moreover, in line with our findings, inferior and superior parietal lobules as well as occipital regions have been implicated in location processing of OLM in earlier studies (for reviews see Postma et al., 2008; Zimmermann & Eschen, under review). The activity decreases between post and follow-up assessments can be ascribed to neural correlates of less proficient performance after training completion. Conversely, a reduction of brain activity in control-related networks of fronto-parietal regions of the left hemisphere (superior frontal gyrus, middle frontal gyrus, frontal pole, inferior parietal lobule) was observed, indicating a decreased demand for executive control processes across time for the completion of the In-scanner OLM task despite continuous performance improvements. The middle frontal gyrus as well as the superior frontal gyrus have been attributed to OLM encoding in young adults (Cansino et al., 2002; Hales & Brewer, 2013). Together, these activation patterns are in line with findings of

trajectories of increased performance as a function of practiced tasks (Kelly & Garavan, 2005).

Brain regions differentially affected by the OLM training and temporal trajectories of their changes across all measurement points

While our longitudinal study design allowed to distinguish between effects on brain activity during both OLM encoding and OLM retrieval, only during OLM encoding differential activation trajectories for both groups across time were observed. This finding makes sense in the light that the intentional encoding of object-location associations can be more willfully affected than their recognition and improvement of encoding leads to better recognition (e.g., Bernstein, Beig, Siegenthaler, & Grady, 2002).

For brain regions differentially affected by the OLM and OLP training across time, we expected for OLM participants increased activity in the first part of the training in brain regions involved in control mechanisms followed by decreased activity in the second part of the training. Congruently, we anticipated in OLM specific regions initial increases in activity followed by decreases due to progressive automation of task-inherent processes. In general, we observed reduced activity in relation to the implicit visual fixation baseline. The reason therefore may lie in the visual fixation cross which, for signalizing the beginning of the encoding phase, turned green 2000 ms beforehand. In anticipation, participants may have responded with increased activation in relation to the activity required for the actual encoding. This anticipation effect before a cognitive task has been reported in previous studies (e.g., Murtha, Chertkow, Beauregard, Dixon, & Evans, 1996). Our hypotheses were confirmed insofar as we observed selective BOLD decreases in the OLM compared to the CON group during the training period. However, these decreases were seen continuously across training in brain structures critically involved in networks of cognitive control such as the bilateral

ACC and the left insula rather than in the inferior temporal gyrus/fusiform gyrus, posterior parietal cortex, and hippocampus. The latter brain regions have been identified as OLM relevant in young adults (Zimmermann & Eschen, under review). In the right PCC however, the expected brain activation pattern of an initial increase followed by a decrease in the second part of the training could be confirmed.

The involvement of the ACC in encoding of OLM has been found in previous studies in young adults (Hales & Brewer, 2013; Sommer et al., 2005b) as well as in healthy older adults (Kukolja et al., 2009). While this structure has been related to top-down control, i.e., controlled information processing (for reviews see Botvinick, Cohen, & Carter, 2004; Bush, Luu, & Posner, 2000), it has also been proposed that the ACC is involved in projecting processed sensory inputs to cognitive and effector regions and thus mediates the functioning of these brain regions. Moreover, to corroborate its proactive role, it has been suggested that ACC activations occur particularly at very early learning stages. Therefore, by mediating requirements and monitoring their fulfillment, the ACC guides the processing of other brain regions (for a review see Weston, 2012). Importantly, while interconnected with the PFC, the ACC also closely interacts with the insula (Weston, 2012), a brain region which has been found to be involved in OLM (Cansino et al., 2002; Meulenbroek et al., 2010). The network model of insula function emphasizes its role in the detection of salient stimuli and the initiation of adequate control signals to regulate behavior. Moreover, this structure has been implicated in top-down cognitive control and in mediating the interactions of networks involved in both in externally orientated attention as well as in internally oriented cognition (Seeley et al., 2007). Together with the ACC, the anterior insula forms the so-called salience network by filtering the most relevant among internal and external stimuli to generate appropriate behavioral responses by integrating bottom-up attention switching with top-down control (for a review see Menon & Uddin, 2010). We found continuous reduction of activity

in the left ACC (dorsal cognitive division) and the left insula in the OLM training group across training with a slight increase at follow-up assessment. For the OLP training group, the respective activation pattern was reversed with an increase from pre- to post-training followed by a slight decrease in these structures four months later. Taken together, for the completion of the In-scanner OLM task, the OLM training group increasingly learnt to direct its focus on the association of objects and their locations and as a consequence had to rely less on attentional-control network structures across the training period followed by a slightly increased demand at follow-up. The opposite pattern was observed for the OLP training group, indicating that increased activity was recruited for the completion of the same task.

Furthermore, in contrast to OLP training participants who demonstrated an activity decrease in the first part and an increase in the second part of the training, we observed in OLM training participants an initial activity increase followed by a continuous decrease until follow-up in the right PCC. While the ACC has been described as executive in function, the PCC has been characterized as evaluative (Bush et al., 2000). Moreover, the PCC is functionally connected to mediotemporal structures (e.g., Greicius, Supekar, Menon, & Dougherty, 2009; Sugiura, Sha, Zilles, & Fink, 2005) and as such has been implicated in episodic memory processes in several studies (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Wheeler & Buckner, 2004; Yonelinas, Otten, Shaw, & Rugg, 2005). Congruently, its critical role has also been reported for OLM (Owen et al., 1996a). Hence, although generally involved in episodic memory, the initial increase in the first part followed by a decrease in the second part of the training is in accordance with expected BOLD signal changes in task-inherent regions. The progressive activity decreases until follow-up were also seen in the right ACC, however without the increase in the first part of the training, indicating that even less cognitive resources were required to complete the OLM task at follow-up. The opposite was observed for OLP training

participants, who obviously had to rely more on cognitive control processes to complete the In-scanner OLM task.

Brain regions differentially affected by the OLM training and temporal trajectories of their changes across two measurement points

Interaction effects for two consecutive measurement points only revealed for OLM training participants activity decreases in the first part of the training in the left ACC and in the second part of the training a decrease in the right hippocampus and the left temporal pole. In contrast to our hypotheses, we did not find activity increases in these regions in the first part of the training. We ascribe this fact to the particular time point in the training at which brain activity was assessed. If participants had been scanned earlier than after three weeks of training, we might have been able to capture initial increases which we only observed in the right PCC. Although these initial activity increases were present in the right hippocampus and the left temporal pole, group x time interactions did not reach significance. However, in line with our hypotheses, the data revealed decreased hippocampal activity for OLM training participants. Evidently, object-location binding became progressively more automatic due to more extensive training, yielding increased neural efficiency. The brain activation changes of OLP training participants in the opposite direction make sense in the light that they did not particularly practice the required ability of associative processing. The involvement of the hippocampus in OLM has been reported in lesion studies (Kessels et al., 2001) as well as in neuroimaging studies with young and healthy older adults (Cansino et al., 2002; Kukolja et al., 2009). A similar activation pattern was observed for the left temporal pole. Neuroimaging studies have emphasized the role of the anterior temporal lobe in semantic memory (Bonner & Price, 2013). Located anterior of the superior, middle, and inferior temporal gyri, the temporal pole is the most rostral portion of the temporal lobe. As a consequence, some of the

activations observed could be ascribed to the rostral temporal neocortex such as inferior and middle temporal areas. On this view, brain regions of the ventral visual processing stream and in particular the inferior temporal gyrus have been demonstrated to be involved in object processing in previous lesion studies (Postma et al., 2004, 2008) as well as in fMRI studies with young adults (Cansino et al., 2002; Johnsrude et al., 1999; Moscovitch et al., 1995) and with healthy older adults (Meulenbroek et al., 2010). Moreover, the anterior temporal lobe has been proposed to be involved in the encoding of information about conceptual properties of objects and is thus fitting within a broad theoretical framework of perception and memory (Bonner & Price, 2013). Despite improved accuracy in the In-scanner OLM task, we observed an activity decrease in this structure in the second part of the training which may relate to a decreased need of object processing and semantic object analysis in favor of object-location binding for OLM training participants, whereas the opposite was true for OLP training participants. Hence, while the process-based training of OLM evoked activity reduction in brain regions involved in control and attentional mechanisms already in the first half of the training, regions more specific to OLM responded at a later stage of the training to repeated task experience.

Between post and follow-up assessments no further interaction effects were observed. Therefore, the maintenance of training-induced effects observed on a behavioral level did neither involve the recruitment of additional brain regions nor the differential activation of already recruited structures, thus indicating a potential consolidation process of the underlying neural mechanisms of OLM due to its extensive practice over six weeks.

Conclusion

Taken together, we provide evidence of plasticity induced by a process-based OLM training in old age. Generally, our findings suggest that the underlying mechanisms of

episodic memory follow a similar pattern as a function of performance-adaptive training as has been reported for process-based training of executive functions. However, due to multiple assessments during a long training period, we were able to follow training-related activation changes more precisely than pre and post assessments allow for. While we confirmed the role of OLM relevant brain regions, our findings support age-comparative studies indicating that older adults activate OLM relevant brain regions less strongly than young adults, but activate them instead contralaterally or recruit further frontal, temporal as well as subcortical brain regions which have not been found to be involved in OLM encoding in young adults (Zimmermann & Eschen, under review). This may reflect the additional effort of older adults to succeed in OLM encoding. Moreover, the recruitment of the anterior temporal lobe during encoding may indicate their attempt to draw on semantic strategies to complete the OLM tasks.

Surprisingly, we found no interaction effects during the recognition phase. The implementation of a cued recall task may have evoked an increased BOLD signal and thus enabled us to differentiate between the two training groups also during retrieval. However, associative recognition as implemented in our study generally evokes similarly widespread activity as cued recall of OLM (Zimmermann & Eschen, under review). Furthermore, the blocked design prevented us from distinguishing correct from incorrect responses which consequently could have shed light on the relationship between encoding and subsequent memory retrieval success. Moreover, to capture the initial activity increase in hypothesized brain regions, the second fMRI assessment would possibly have been more appropriately scheduled after one rather than three weeks of training as had been done in the study by Kühn and colleagues (2013) who reported an inverse u-shape function with related brain activity to training over time.

In conclusion, knowledge as provided in our study can facilitate a better understanding of brain changes in response to cognitive interventions on multiple levels, i.e., the underlying mechanisms of training-related changes across time which would remain undetected if only investigated on a behavioral level. Furthermore, brain imaging across several time points allows the capture of different learning stages in the course of a training and offers not only information as to which brain regions respond to training, to what degree, but also at what point in the training intervetion. On that view, it would be of interest to investigate how training gains are linked to brain activation changes and if they are related to the effect of performance improvements. Attending to these factors will help to explain the particular activation patterns observed and to distinguish between the mechanisms likely to be underlying those changes.

6 GENERAL DISCUSSION

In the first part of this chapter, the main results of the three articles of this thesis are summarized and discussed separately. Furthermore, their limitations are outlined followed by suggestions on how to resolve them in future studies. In the second part of this chapter, the findings of the three articles are integrated into the broader literature on cognitive training in older adults, and training-induced cognitive as well as neural effects and implications for future research with respect to theoretical, methodological, and practical aspects are discussed.

6.1 Article 1 – Brain Regions Involved in Object-Location Memory Across Adulthood: What do We Know and What is Missing?

The aims of the first study were to identify brain regions specific to object-location memory (OLM), to examine their changes across adulthood, and to acquire knowledge of functional changes induced by training interventions targeting OLM. To this effect, we reviewed evidence from 31 empirical studies, 16 of which provided findings from patients with focal brain lesions and healthy controls, whereas the other 15 were neuroimaging studies conducted with healthy adults. In addition to young adults, three of these studies included healthy older participants and thus allowed for age-comparative findings. Neither longitudinal studies on brain changes across adulthood nor relevant OLM training studies were found, thereby highlighting an obvious research gap.

The main findings of this review are as follows: Both lesion and neuroimaging studies of young adults indicated the involvement of the inferior temporal gyrus, the posterior parietal cortex, and the parahippocampal gyrus in OLM. While the lesion studies pointed to the specific contribution of anterior/mediotemporal regions in OLM, and in particular emphasized the role of the hippocampus, the neuroimaging studies also revealed the recruitment of

frontal, cerebellar, and occipital regions in OLM. Moreover, the three age-comparative neuroimaging studies suggested that older adults activated relevant brain regions less strongly than young adults. Instead, they recruited relevant brain regions in the contralateral hemisphere or additional frontal, temporal, or subcortical brain regions.

Limitations of this first article mainly concern the methodological weaknesses of some of the reviewed studies. The vast number of lesion studies did not include any procedure to ensure the health status of control groups, nor did they report if they were matched to the included patients with respect to relevant variables. Furthermore, patients in some lesion studies were not screened for essential criteria such as handedness, perceptual deficits, or the exact extension of their lesions. Besides, most patients had been suffering from epilepsy before undergoing surgery which could have resulted in the functional reorganization of the brain. Also in the neuroimaging studies with young adults, participants were not always carefully screened for health. Consequently, these inconsistencies had to be taken into account for the interpretation of the findings of these particular studies. Moreover, in the lesion studies, patient groups comprised mostly small samples, thus the power of statistical analyses was low and the interpretation of results problematic. These limitations could be overcome in future studies by recruiting larger samples of patients, by assessing the extent of their lesions more thoroughly, and by matching patients more carefully to control participants, who in turn had been screened elaborately for relevant variables such as handedness and health status. However, the potential functional reorganization of patients' brains cannot be eliminated since reactive plastic alterations are inherent, and restoring or compensatory reactions after brain damage commonly occur (e.g., Chen, Cohen, & Hallett, 2002; Rossini, Calautti, Pauri, & Baron, 2003).

In addition, while the findings of the lesion studies mainly concerned mediotemporal regions – in particular the hippocampus – due to the included samples of patients with lesions

within these structures, the neuroimaging studies also indicated differential specialization of the inferior temporal gyrus/fusiform gyrus, the posterior parietal cortex, the parahippocampal gyrus, frontal and occipital regions, and the cerebellum for OLM functioning. These contradictions can be attributed to methodological differences. On the one hand, the neuroimaging studies were superior for the detection of brain regions other than mediotemporal structures, i.e., brain regions specific to subprocesses of OLM. On the other hand, they were less sensitive in separating small structures such as the hippocampus and the parahippocampal gyrus within the medial temporal lobe (MTL) due to limited spatial resolution as well as magnetic susceptibility artifacts in this region. However, by combining both evidence from lesion and neuroimaging studies – as has been done in this first article – the limitations of each source have been overcome and converged to provide valuable insights into the neural networks of interest.

Another limitation is the fact that the reviewed neuroimaging studies only investigated OLM tasks within categorical spatial relations, while the lesion studies also included coordinate OLM tasks. In addition, only two studies manipulated the demands on egocentric versus allocentric location processing. Given that in real life situations objects need to be processed under a high variation of viewpoints, different spatial relations have to be applied for efficient processing. Following Kosslyn and colleagues (1987, 1992), categorical relations form general, abstract codes and capture basic and invariant spatial information without the definition of exact metric parameters. In contrast, coordinate spatial relations specifically describe the spatial location of an object in terms of exact distances. Thus, if objects are perceived in various positions, categorical processing is helpful by establishing general and abstract spatial relations between them. In turn, if objects are perceived in a viewpoint-dependent manner, metric-coordinate information is used for the performance of direct motor actions towards these objects, i.e., by reaching for a glass on the table. Hence, there seems to

be a relationship between how stimuli are presented and how they are processed with respect to spatial relations (categorical/coordinate) and reference frames (egocentric/allocentric). Along these lines, it has been suggested that participants favor allocentric location processing when target objects are positioned in a regular manner (e.g., a grid) and egocentric location processing when target objects are arranged in an irregular fashion. While spatial relations (categorical/coordinate) and reference frames (egocentric/allocentric) appear to represent distinct processes, they may interact when task characteristics such as task difficulty are changed. Furthermore, it has been proposed that categorical and coordinate spatial relations are lateralized and thus engage different neural mechanisms, however negative findings also need to be taken into account (Jager & Postma, 2003). Consequently, the lack of variation in OLM tasks in the reviewed neuroimaging studies may have provided a too narrow perspective on differential location processing. However, prospective studies can address this issue by implementing paradigms apt to explicitly distinguish between these processes in order to clarify existing findings as to the hemispheric specialization of categorical and coordinate processing as well as to pursue a deeper understanding regarding the relationship between spatial relations and reference frames.

Despite the aforementioned limitations, our review of OLM was the first to include evidence from neuroimaging studies in addition to findings from lesion studies to such a large extent. Overall, it confirms many proposals of the neurocognitive model of OLM by Postma and colleagues (2004, 2008). In particular, it approves the specialization of the inferior temporal gyrus/fusiform gyrus for object processing and the posterior parietal cortex for location processing. The reviewed lesion studies also support the proposal that the hippocampus specifically supports object-location binding and allocentric location processing. Due to the included neuroimaging studies, this review also provides considerable new knowledge concerning the interplay between brain regions involved in OLM and points

to the critical roles of supplementary regions in subprocesses of OLM, namely the parahippocampal gyrus for object memory, frontal regions (superior and middle frontal gyrus) for OLM encoding, and occipital regions for additional visual perceptual effort for processing object-location associations compared to processing objects or locations alone. Furthermore, cerebellar regions have been found to be implicated in viewpoint-independent location processing.

With respect to age-related differences, older adults have been found to recruit other brain regions than young adults such as the anterior cingulate gyrus, the left superior temporal lobe, basal ganglia regions, and the thalamus, indicating that they also apply differential strategies (possibly semantic or temporal order strategies) to complete OLM tasks. Finally, this review provides meaningful suggestions on how OLM in old age could be best trained and which brain regions should be targeted to mitigate its typical decline.

6.2 Article 2 – Transfer Effects of a Process-Based Object-Location Memory Training in Old Age: A Double-Blind Randomized Controlled Trial

The aims of this empirical study were to examine whether OLM can be enhanced by extensive practice in healthy older adults and to unveil characteristics of individuals for whom this training is particularly suitable. To this effect, we investigated the efficacy of a six-week process-based OLM training in terms of training gains, transfer, and maintenance. A group of 27 older adults received an adaptive object-location memory training (OLM; experimental group) and 24 older adults completed a structurally similar non-adaptive visual object-location perception training (OLP; active control group). All participants were administered a cognitive test battery measuring spatial episodic memory for near, verbal episodic memory for medium, and reasoning for far transfer. Transfer distances were categorized according to the taxonomy by Noack and colleagues (2009), and tests were conducted before, in the

middle, and immediately after the training as well as four months later. We hypothesized that OLM performance would increase linearly across the training period and that training effects would be medium to large (Hampstead et al., 2012a; Noack et al., 2013). In the light of existing findings on process-based training in healthy older adults (Lustig et al., 2009), we expected that compared to the participants of the OLP training group, the OLM training group would improve at least in near transfer performance during the training period, and that these effects would be largely maintained from post to follow-up measurement. In addition, we anticipated training participants' characteristics, in particular motivational factors, to be positively associated with training success (e.g., Jaeggi et al., 2014).

The main findings of this study comprise evidence of the feasibility and efficacy of a process-based OLM training with older adults. A significant linear increase in training task performance across 30 sessions was observed in the performance-adaptive OLM training condition. Analyses addressing training-related changes in untrained tasks revealed significant near, but not medium or far transfer for the OLM training compared to the OLP training participants. Near transfer effects were maintained from post-training until four months after training termination. Together, the present study demonstrated that a process-based OLM training improved its targeted task but also other spatial episodic memory abilities enduring in older adults. Moreover, we uncovered differences in participants' pre-existing attributes, i.e., higher scores in expected training success, initial spatial associative episodic memory ability (near transfer composite), crystallized intelligence, and openness to experience, which may indicate why some individuals profited more from the training than others. For episodic memory, empirical evidence is mixed as to whether individuals with high levels of task-relevant cognitive resources gain more or less from training than individuals with low initial cognitive ability (Kliegl et al., 1990; Verhaeghen & Marcoen, 1996; but see Jaeggi et al., 2008; Karbach & Kray, 2009; Zinke et al., 2011). As a consequence, the diverse findings have

given rise to controversial discussions on interindividual differences in training gains, thus, the two main competing views need to be addressed. The magnification view suggests that differences in training gains can be explained by initial differences in cognitive resources to acquire and implement effortful strategies to ameliorate cognitive processes. In contrast, the compensation view indicates that individuals with high initial cognitive abilities are already functioning on an optimal level and accordingly have less room for improvement (Lövdén, Brehmer et al., 2012). Participants in our study who profited most from the training demonstrated high initial spatial associative episodic memory performance. Hence, our findings support evidence that individuals with high levels of resources in the to-be-trained domain are more likely to increase their abilities and to an even greater extent than individuals with low initial ability, suggesting that individuals with a high cognitive status may have a greater potential for cognitive plasticity.

The lack of a criterion task may be viewed as a limitation of this study. Because it is unlikely that all individuals exhibited similar initial capacity for the to-be-trained tasks, it is possible that participants had to train below their limits, that is, below their functional capacity for several training sessions before they reached the optimal mismatch of supply and demand. Thus, the operationalization of training gains in terms of reached difficulty levels may have been confounded by the individuals' inherent capacities and as a consequence resulted in the achievement of higher task difficulty levels even if actual training gains were absent. The implementation of a criterion task (similar in structure to the experimental training tasks but different in stimulus material) before and after the training intervention generally helps to quantify training improvements more accurately (e.g., Brehmer et al., 2012; Dahlin et al., 2009). However, for pragmatic reasons we refrained from doing so. Besides, it remains unclear whether a criterion task would have provided further insights since the initial OLM training capacity (mean percentage of correctly recalled object-location associations in

the three training tasks in the first training session) did not discriminate between low and high training gainers in our study.

Another limitation concerns the sample of this study. The present study included young-old adults who were highly educated which makes the detection of training effects more likely. In addition, if the aim is to train not task-specifically but to impact the construct underlying the task, namely the cognitive ability, then training-related changes should be analyzed on a latent level, e.g., with structural equation modeling or latent change score models (Noack et al., 2014). Yet, even analyzed on a latent level, the question remains how non-cognitive factors such as motivational factors can influence training effects (Shipstead, Redick, & Engle, 2010). To resolve this problem, challenging training paradigms for both experimental and active control groups should be implemented. Indeed, one must ensure that the two trained abilities are not associated with regard to the targeted transfer construct. In other words, while the control training should not lead to improvements in the experimental training tasks nor the targeted transfer construct (discriminant validity), the experimental training should enhance performance in both the trained tasks as well as the transfer construct (convergent validity) (Noack et al., 2014). Unfortunately, the sample size of the study described in the second article did not allow for analyses on a latent level. However, these limitations could be overcome in future studies by including a larger sample and by attempting to recruit a more diverse participant pool with regard to age and educational level.

In conclusion, this empirical study documented the first evidence of the efficacy of a process-based OLM training with regard to training gains as well as immediate and long-term training-induced near transfer effects. In fact, our study participants were able to maintain training-induced effects across four months. Obviously, this training approach has the potential to ameliorate episodic memory decline in older adults to the extent of transferability to closely related untrained tasks of the same narrow memory ability. Moreover, our findings

suggest that motivation at baseline is a key factor contributing to training success in old age. Motivation has been strongly linked to self-efficacy, i.e., an individual's judgment of his or her capabilities to perform a given action (Zimmerman, 2000). Participants in our study who expected the training outcome to be successful possibly appraised their own capabilities as high, consequently strived to a greater extent for maximum performance, and as a result accomplished larger training gains. Importantly, the way one perceives a learning situation can be influenced. Therefore, it would be meaningful to increase interest and raise positive attitudes towards new learning experiences. To keep older adults motivated once signed up for a cognitive training, it is vital to ensure that they can succeed during the training. This could be achieved by adjusting task difficulty, by providing appropriate feedback and – especially in training interventions using new or unfamiliar technologies – by making extensive support available.

In sum, this study offers a new understanding in terms of theoretical considerations with regard to the efficacy of different training approaches as well as to their practical relevance and thus provides the necessary ground for future research on this special type of memory training.

6.3 Article 3 – Neural Plasticity Induced by a Process-Based Object-Location Memory Training in Healthy Older Adults

The aims of this empirical study were to identify brain regions affected by a process-based OLM training in old age, and in particular, to explore training-related brain activation changes over time. For this purpose, we analyzed functional magnetic resonance imaging (fMRI) data of an untrained In-scanner OLM task acquired as part of the study discussed in the second article of this thesis. Assessments took place before the training, in the middle of

the training, immediately after the training was completed as well as four months later at follow-up.

In the light of existing findings on training-induced activation patterns at multiple stages during the training period (Hempel et al., 2004; Kühn et al., 2013), we expected to observe initial activity increases in the first part of the training followed by decreases in the second part of the training in brain regions involved in cognitive control processes such as the prefrontal cortex (PFC) as well as in OLM relevant brain regions due to a shift from effortful processing to more automatic processing after more extensive training. From post to follow-up assessment we hypothesized a general activity increase in these regions.

The main findings comprise training-related neural changes across the study. Because the OLM training group showed significantly larger improvements in the In-scanner OLM task over time compared to the OLP training group, fMRI analyses were conducted independently from the In-scanner performance. Across all four measurement points, similar activation changes (main effect of time) were observed in both training groups in several brain regions during encoding and recognition. We found increased activity during the training period followed by slight decreases at follow-up in occipito-parietal regions which are relevant for the perception of visuo-spatial stimuli, i.e., the stimuli material used in both training regimes. Conversely, continuous reduction of brain activity in control-related networks of fronto-parietal regions was observed, indicating a decreased demand on control processes across time for the completion of the untrained In-scanner OLM task despite continuous performance improvements. Together, these activation patterns are in line with findings on increased practice-related performance during the training period and less proficient performance after training completion (Kelly & Garavan, 2005).

Furthermore, interaction analyses during encoding revealed significant differential brain activation trajectories for the two groups across the whole study period. Compared to the OLP

training group, the OLM training group demonstrated continuous reduction of brain activity across training in control regions proactively influencing the fulfillment of cognitive requirements (bilateral anterior cingulate cortex (ACC), left insula) followed by a slight increase at follow-up. While the dorsal ACC (cognitive division) has been related to controlled information processing (Botvinick et al., 2004; Bush et al., 2000), it also closely interacts with the insula (Weston, 2012), a structure which has been implicated in top-down cognitive control and in mediating the interaction of networks involved in both externally oriented attention as well as in internally self-related cognition (Menon & Uddin, 2010). In addition, we observed an initial activity increase followed by a continuous decrease until follow-up in the right posterior cingulate cortex (PCC), a brain region functionally connected to mediotemporal structures (e.g., Greicius et al., 2009) which have been found to be involved in episodic memory processes (e.g., Eldridge et al., 2000; Yonelinas et al., 2005) and in OLM (Owen et al., 1996a). Separate interaction analyses for two consecutive measurement points yielded significant activity decreases in the second part of the training in the right hippocampus and the left anterior temporal lobe (temporal pole) for OLM compared to OLP training participants. Since the hippocampus has been implicated in object-location binding (e.g., Kessels et al., 2001), this process may have become more automatic with more extensive training in participants of the OLM training group, a finding in accordance with increased neural efficiency. The temporal pole is the most rostral portion of the temporal lobe. Consequently, some of the activity observed could be ascribed to inferior and middle temporal areas. While brain regions of the ventral visual processing stream (i.e., the inferior temporal gyrus) have been found to be critically involved in object processing in both lesion and neuroimaging studies (Postma et al., 2008; Zimmermann & Eschen, under review), the anterior temporal lobe has also been reported as a region to encode information about conceptual properties of objects and as such fits well within a broad theoretical framework of

perception and memory (Bonner & Price, 2013). For participants of the OLM group, the observed activity decrease in this structure in the second part of the training thus may relate to a decreased need of object processing and semantic object analysis in favor of object-location binding.

Surprisingly, we did not detect interaction effects during recognition. A cued recall task whereby participants would have been asked to actively relocate the encoded stimuli to their correct locations by button presses corresponding to the coordinates in the grid (A1, A2, A3, B1, etc.) might have evoked an increased BOLD signal. Consequently, we would have been able to differentiate between the two training groups during both encoding *and* retrieval phases. However, instead of a 5x5-grid as used in our study, a grid not bigger than 3x3 would have had to be employed in order to keep the task manageable. This in turn would have left fewer possibilities for the presentation of object-location associations. Obviously, it is challenging to find the ideal level of task difficulty to assess both memory phases optimally.

Furthermore, the blocked design prevented us from distinguishing correct from incorrect responses which consequently could have shed light on the relationship between encoding and subsequent memory retrieval success.

While the implementation of four measurement points enabled us to investigate training-induced brain activation changes longitudinally, the time point of the second fMRI assessment was possibly not ideally chosen to capture the initial activity increase in hypothesized brain regions. Hence, future studies which are especially interested in early learning stages should address this issue by implementing an additional fMRI session early in the training. Moreover, to better understand how training-associated performance gains relate to brain activity, it would have been interesting to investigate the brain-behavior relationship in more detail.

In conclusion, this study provided evidence on neural plasticity induced by a process-based OLM training in old age. While our findings suggest that training-related brain activity of episodic memory follows a similar pattern as has been reported for process-based training of executive functions (e.g., Brehmer et al., 2011; Dahlin et al., 2008), we were able to observe temporal trajectories of brain activation changes more closely than pre-post-designs allow for. In addition, our findings were congruent with age-comparative studies discussed in the first article of this thesis which reported that older adults activated OLM relevant brain regions contralaterally or to a lesser extent than young adults or even recruited additional brain regions (Zimmermann & Eschen, under review). Altogether, these findings may reflect the differential use of strategies in older adults to complete OLM tasks and/or their additional effort to successfully encode object-location associations. Hence, knowledge as provided in our study can facilitate a better understanding of brain changes in response to cognitive interventions on multiple levels, i.e., the underlying mechanisms of training-related changes across time which would remain undetected if obtained on a behavioral level. Furthermore, brain imaging in several time windows allows the capture of different learning stages in the course of a training and thus offers not only information as to which brain regions respond to training and to what degree, but also at what point in the training phase. In conclusion, further attention to these factors will help to explain the particular activation patterns observed and to distinguish between the mechanisms likely to be underlying those changes.

6.4 Implications of Current Thesis for Future Research

In the following section, the findings of the present work are integrated and discussed with respect to broader methodological, conceptual, and practical implications for cognitive training interventions in older adults. The scope includes the transfer of cognitive training, the contribution of pre-existing interindividual differences to training success, the role of

intraindividual variability in association with cognitive performance as well as the relationship between age-related structural and functional changes with regard to future training studies aiming to suit individuals' needs. The chapter closes with final conclusions.

Overall, the three articles of this thesis provided new insights into a type of memory that – despite its high functional relevance – has been understudied so far. The systematic review revealed brain regions specific to OLM, age-differences in recruiting these structures while completing OLM tasks and following from this also implications for training interventions targeting OLM in healthy older adults. The findings of the second article demonstrated that a process-based training improved OLM performance in healthy older adults in terms of training gains, transfer, and maintenance. Moreover, pre-existing characteristics such as motivational factors were uncovered which may indicate why some individuals profited more from the training than others. Finally, the third article highlighted which brain regions were affected by the process-based training as well as brain activation changes during the training period until four months later.

With regard to extending knowledge about OLM and its plasticity, findings of the first article imply that older adults generally recruited brain regions that had not been involved when young adults solved OLM tasks, and if they were involved, older adults activated these structures to a greater degree in the contralateral hemisphere or recruited brain regions engaged in networks of cognitive control. However, their attempts to solve OLM tasks by applying differential strategies such as semantic or temporal order strategies proved to be inefficient since they performed worse than young adults. These findings are in line with the two major patterns of activation differences between young and older adults (HAROLD: Cabeza, 2002; PASA: Davis et al., 2008). Furthermore, the second article indicates that a process-based training of OLM was not only feasible but induced significant training gains in the trained tasks and near transfer to untrained spatial epsiodic memory abilities in older

adults. Moreover, transfer effects were maintained until at least four months later, illustrating the training's potential to impact the underlying mechanisms in a sustained manner. Finally, the third article suggests that brain activation changes induced by a process-based episodic memory training followed a similar pattern which has been reported for training interventions targeting executive functions by means of activity decreases from pre- to post-training in task-relevant brain regions (Brehmer et al., 2011; Dahlin et al., 2008). Moreover, the additional assessments of brain activation changes in the middle of the training and at follow-up unveiled the temporal progression of induced neural plasticity. Together, the combination of behavioral and neuroimaging assessments proved to be suitable to single out cognitive and neural effects. Furthermore, the use of fMRI enabled the disentanglement of different phases of the memory process, i.e., the intentional encoding of object-location associations as well as their recognition which cannot be obtained by behavior alone. Generally, fMRI assessments offer insights about cognitive processes which may have been differentially engaged to perform the task even though individuals show similar behavioral patterns. Importantly, brain imaging is also an excellent tool to identify brain regions which are sensitive to cognitive training and to provide knowledge that can be used to predict tasks for which training is most likely to be transferable (Lustig et al., 2009).

From laboratory to real life situations

One question that needs to be addressed is whether and how cognitive training interventions conducted in the laboratory translate into real life situations. In other words, do they merge with daily life situations of older individuals? Obviously, it is desirable that transfer does not only apply to untrained tasks but to tasks and affordances that older individuals have to deal with on a daily basis. Practically, to overcome the gap between the laboratory settings of psychological interventions and everyday competence, several avenues

of research could possibly be taken. One route could be that training tasks of an OLM training reflect everyday OLM tasks – identified to be relevant by older adults themselves – to a greater degree than they do so far. For instance, instead of encoding objects and their locations in a grid, participants could train object-location associations in virtual reality environments simulating the real world. This has already been done in the studies by King and colleagues (2002, 2004) where objects had to be remembered in a courtyard (see first article in this thesis). Moreover, in one of the spatial training tasks in the study by Hötting and colleagues (2013), participants were also presented with a virtual courtyard surrounded by distinct walls which could be used as landmarks to memorize the locations of five objects which appeared sequentially. After a distractor phase, each object's location had to be retrieved from a large number of location possibilities. The retrieval phase was presented from the same viewpoint as during encoding or in one of three shifted viewpoints (i.e., 60^{o}, 120^{o}, 180^{o}). Although a courtyard may not perfectly resemble typical daily life situations of older individuals, the paradigm could be transferred to any room (e.g., kitchen, living room) in a house.

It is important to note that this thesis focused on OLM acquired from a static viewpoint and in reference to one's own body, that is within an egocentric frame of reference. This ability is clearly required in small-scale surroundings for remembering where we have stored personal belongings in the house. However, in large-scale environments when searching for the parked car or the favorite restaurant in the neighbourhood, OLM acquired by navigation becomes more appropriate. Along these lines, Lövdén, Schaefer and colleagues (2012) employed a virtual environment in which healthy younger and older particpants acquired OLM not from a static viewpoint but rather by spatial navigation. Although not implemented in training studies, other virtual reality paradigms have been used to locate and retrieve household items in a small virtual grocery store (Spiers, Sakamoto, Elliott, & Baumann,

2008) and for the recognition of objects' locations (toys or office supplies) in a museum (Janzen, 2006; Janzen & van Turennout, 2004). Because these settings resemble real life situations to a greater degree than grids or arrays, they have an increased potential of transferability to tasks with which older individuals are confronted with on a daily basis. Hence, virtual reality paradigms could also be useful for the investigation of OLM as defined in this thesis. Despite the differences between a training of OLM acquired from a single perspective and a training targeting OLM acquired by navigation, it would be interesting to explore whether a training of OLM acquired from a static viewpoint also benefits navigational skills whereby different viewpoints of objects and their locations need to be integrated and vice versa. Clearly, future studies should continue to investigate whether cognitive training can alleviate age-related changes and their underlying neural substrates but also further appraise the transfer from laboratory to life.

Interindividual differences

Another highly salient issue is whether the goal of cognitive training is to improve function or minimize loss, that is, the attempt to slow cognitive aging. In other words, should cognitive training intend to remediate cognitive deficits or rather improve compensational mechanisms by focusing on abilities that are less affected by normal aging? The discussion of these issues leads to another closely related question, namely, whether it is meaningful to pursue training approaches of "one size fits all" or whether they should be tailored to specific individual situations or needs (Ranganath et al., 2011). Obviously, the optimal intervention depends on the individuals who are to be targeted. Older adults signing up for training interventions often differ considerably in terms of cognitive abilities, resources, deficits, goals, and expectations. Therefore, customized training is clearly appropriate and should be implemented when addressing individuals with specific claims and needs.

Generally, there are substantial individual differences in cognitive decline with respect to onset and rate (Nyberg et al., 2012; Wilson et al., 2002). To explain possible mechanisms that could account for these differences, several models have been proposed. For instance, the cognitive reserve model implies that certain behaviors and experiences such as education and maintenance of an active lifestyle result in an increased supply of neural resources that can protect from and delay age-related decline (Stern, 2012). On the contrary, the scaffolding theory of aging and cognition (STAC; Park & Reuter-Lorenz, 2009) assumes that cognitive training or prolonged engagement in a novel task or environment can enhance the development of compensatory scaffolding by recruitment of additional neural activities in support of brain functions that have become inefficient. Plasticity will manifest itself as a consquence of a sustained mismatch between a person's desired cognitive state, the environmental demands (Lövdén et al., 2010), and most importantly by the individual acting on it (Park & Bischof, 2013).

In addition, there is also substantial interindividual variability in the effects of cognitive training, i.e., individual differences in the amount of training gains are considerably large (Bissig & Lustig, 2007). In particular, older adults markedly differ in how much they profit from cognitive training to the extent that individuals who need the training the most typically benefit the least (Lustig & Flegal, 2008). First attempts to gain better knowledge of these differences have been made by studies identifying pre-existing abilities such as crystallized intelligence, need for cognition, personality traits, motivational factors, or cognitive status which may at least partly explain why training interventions are beneficial to some individuals but not to others (e.g., Bissig & Lustig, 2007; Jackson, Hill, Payne, Roberts, & Stine-Morrow, 2012; Jaeggi et al., 2014; Studer-Luethi et al., 2012; see also von Bastian & Oberauer, 2014). With respect to cognitive abilities, the conditions in which the magnification account (high initial cognitive status is associated with large benefits) or the compensation

account (low initial cognitive status is associated with large benefits) occur are still not well understood (Shing, Schmiedek, Lövdén, & Lindenberger, 2012). Congruently, interindividual differences in cognitive status may also account for the direction and magnitude of practice-related brain activation changes (Kelly, Foxe, & Garavan, 2006). Clearly, a better understanding of the reasons for these individual differences would be valuable for the development of effective training regimes that are tailored to individuals' cognitive abilities.

Usually, only the combination of several attributes may explain why some individuals profit more than others from cognitive training. Therefore, the investigation of these interindividual differences could be the first step to gaining a better understanding of the source of interindividual variability in the effects of cognitive training and how these variables relate to performance variability.

Intraindividual variability

Evidently, pre-existing differences may not fully account for the individual's potential for change in performance. Moreover, it cannot be assumed that behavior remains stable and that the trajectories of change are similar for all individuals (Hultsch, Strauss, Hunter, & MacDonald, 2008). On this view, fluctuations of day-to-day variability in motivation or affective experiences within individuals have been linked to intraindividual variability in cognitive performance (Brose et al., 2010; Brose, Schmiedek, Lövdén, & Lindenberger, 2012). The concept of short-term intraindividual variability represents transient within-person fluctuations in emotional state, physical performance, or cognitive processing (e.g., accuracy, processing speed) and must be distinguished from behavioral changes that are more enduring (Hultsch et al., 2008; Li, Huxhold, & Schmiedek, 2004). The relevance of intraindividual variability has been explained in the context of understanding changes in cognitive aging. For instance, short-term intraindividual variability could be viewed as a potential indicator of

cognitive functioning (e.g., high intraindividual variability points to increased noise in neural information processing) and thus help to detect change in cognitive functioning prior to clinically significant changes in performance (Hultsch et al., 2008). Indeed, it has been suggested that high intraindividual variability is likely to reflect a compromised cognitive system (e.g., Li & Lindenberger, 1999) or is indicative of neural changes such as white matter demyelination or lesions to frontal gray matter (MacDonald, Nyberg, & Bäckman, 2006). Increased intraindividual variability has also been observed as less efficient BOLD activations and linked to age-related cognitive impairment (Hedden & Gabrieli, 2004). However, intraindividual variability does not necessarily signal vulnerability. For instance, Garrett and colleagues (2011) found – opposed to mean-based brain measures – that BOLD signal variability was significantly lower in older compared to younger and better performing adults during the completion of cognitive tasks (perceptual matching, attentional cueing), indicating that a more variable brain is a more effective brain. Congruently, it has been suggested that intraindividual variability may be a reflection of learning and strategy modification (Li et al., 2004; Li, Aggen, Nesselroade, & Baltes, 2001). In fact, short-term intraindividual variability and intraindividual change have been proposed to dynamically interact (Hultsch et al., 2008; see also Röcke & Brose, 2013).

In the context of cognitive interventions, the assessment of short-term intraindividual variability is not restricted to cognitive performance but would seem appropriate also in terms of variations in subjectively accessible states such as motivation or affect (Brose et al., 2010; 2012; Röcke, Li, & Smith, 2009). Generally, there are methodological issues to be considered. By using so-called measurement-burst designs (Nesselroade, 1991), key variables can be obtained in fine-grained timescales over a longer period (daily, momentary). Since the magnitude of retest correlations is in proportion to the power required for the detection of significant change, such a design allows for the detection of change over shorter intervals in

fewer individuals than usually required (Sliwinski, 2008). However, it also needs a sophisticated approach to assess these variables (via internet or by electronically operated devices) as well as the appropriate statistical knowledge to analyze this rich but very complex data (e.g., multilevel modeling). Indeed, we had participants in our study declare their current motivation and current emotional states before they started each training session. Motivation was rated on a 5-point Likert scale (1 = not at all motivated; 5 = very motivated) and emotional states on two 9-point Likert scales which were illustrated with Self-Assessment-Manikin (Bradley & Lang, 1994*).* The impending analyses of intraindividual fluctuations in these variables and how they possibly relate to training performance variability will be of great interest.

Altogether, assessing short-term intraindividual variability in the context of cognitive training interventions may provide unique information beyond measures of central tendency which is of critical value to grasp older adults' approach to cognitive performance, their selective strategy use in task processing, their goal setting, their allocation of cognitive resources, and most importantly, how these factors are associated with each other and with older individuals' cognitive performance. Thus, to better grasp the many factors contributing to training outcomes, multiple behavioral as well as neuroimaging assessments in the course of the training are clearly indicated. By monitoring affective, motivational, and volitional dimensions as well as by capturing a wide range of other differential processes (e.g., anticipatory, adaptive, compensatory; Martin & Hofer, 2004), we may continue to gain a better understanding of the mechanisms underlying and/or contributing to individual learning curves and to be able to outline a clearer picture of what an optimal training program for older adults really means. In fact, this may call for modifications such as self-paced completion of training tasks, performance-adaptive task difficulty, or individualized presentation times of stimuli.

Relationship between age-related structural and functional changes

Finally, another road that could be taken is to further explore the relationship between structural and functional plasticity induced by cognitive training. In recent years, there has been an increasing interest in understanding the neurobiological alterations associated with healthy aging as well as their relation to cognitive decline. While age-cognition relations are well established in cross-sectional comparisons, they are increasingly investigated in longitudinal approaches (Salthouse, 2011). However, despite the fact that age-related structural and functional changes mutually interact, i.e., structural changes are accompanied by functional changes and vice versa and a clear segregation is thus not possible, the two processes are usually investigated separately. Indeed, findings on the relationship between functional and structural changes in the context of aging are conflicting and document either no association between structure and function in healthy older adults (Johnson et al., 2000; Madden et al., 2010) or a profile of less structural integrity associated with less activity in PFC regions (e.g., Davis, Kragel, Madden, & Cabeza, 2012). Notably, for memory performance, the relationship between structural and functional brain changes and aging has seldom been investigated nor their unique and combined contribution to age differences. The few existing findings have so far linked age-related structural differences to age-related functional under- as well as over-recruitment in episodic memory performance (Kalpouzos, Persson, & Nyberg, 2012). Congruently, the recent study by Rajah and colleagues (2011) found a positive correlation between a larger volume of the right middle frontal gyrus and greater activity in a commonly found episodic retrieval network for young, but not for older adults. Instead, volume loss in the right middle frontal gyrus was negatively correlated with retrieval-related activity of episodic memory. As for OLM, only three studies have investigated age-related brain activation changes in this type of memory (Kukolja et al., 2009; Meulenbroek et al., 2010; Schiavetto et al., 2002) and only one study also examined age-

related structural changes (Kukolja et al., 2009). However, combining modalities can only enrich our understanding of the aging brain and further help to differentiate between normal and pathological aging. In view of the decline in visuo-spatial memory functioning as one potential precursor of Alzheimer's disease (Alescio-Lautier et al., 2007; Hort et al., 2007), this knowledge may even foster the development of tailor-made cognitive training interventions aimed at mitigating age-related OLM decline beyond healthy aging.

Conclusion

In conclusion, this thesis provides evidence of a new and promising field for the application of process-based memory training. Episodic memory has so far been targeted successfully by *strategy-based* training. However, while the instruction of strategies seems promising in old age, it has been established that older adults generally demonstrate low strategy use (Verhaeghen & Marcoen, 1996) or do not generalize the trained strategy to other than the trained material in their everyday life (Noack et al., 2009). With regard to OLM, a prototypical form of episodic memory, our findings offer reasons for being optimistic that a *process-based* training aproach may have the potential to preserve episodic memory functioning or prolong its decline. In closing, OLM as a highly relevant function for managing daily life deserves more attention in the context of healthy aging than up until now and especially in the light that the fear of losing one's ability to live independently is consistently expressed when adults consider old age (Lustig et al., 2009). Therefore, the knowledge acquired in this thesis should be exploited to maintain and promote cognitive health in old age and to guide the development of interventions customized to the individuals most in need and to areas of high personal relevance to aging individuals.

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Supplementary Material

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